JAN 21 1918

VOLUME 21 NUMBER 1

THE ARCHIVES OF INTERNAL MEDICINE

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago

RICHARD C. CABOT, Boston
THEO. C. JANEWAY, Baltimore
GEORGE DOCK, St. Louis
WARFIELD T. LONGCOPE, New York
W. S. THAYER, Baltimore

JANUARY 15, 1918

CHICAGO
AMERICAN MEDICAL ASSOCIATION
PUBLISHERS

Entered as Second-Class Matter, January 21, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879

CONTENTS OF VOLUME XX

JULY, 1917. NUMBER 1

The Pulse Flow in the Brachial Artery. V. The Influence of Certain Drugs. Albion Walter Hewlett, M.D., San Francisco.

Study of a Case of Diabetes Insipidus with Special References to the Mechanism of the Diuresis and of the Action of Pituitary Extract on It. C. D. Christie, M.D., and G. N. Stewart, M.D., Cleveland.

Multiple Hemangiomas of the Skin Associated with Dyspituitarism. George Douglas Head, B.S., M.D., Minneapolis.

The Study of a Small Outbreak of Poliomyelitis in an Apartment House, Occurring in the Course of an Epidemic in a Large City. Montrose T. Burrows, M.D., and Edwards A. Park, M.D., Baltimore.

The Influence of Splenectomy on Metabolism in Anemia. W. Denis, Boston.

Phthisis Pulmonalis and Other Forms of Intrathoracic Tuberculosis. W. A. Gekler, M.D., Chicago.

The Electrocardiogram; Its Relation to Cardiodynamic Events. Carl J. Wiggers, M.D., New York.

Studies of the Blood in Beriberi. I. Yoshikawa and T. Nemoto, Tokyo, Japan.

A Study of Renal Function in Patients Convalescing from Acute Fevers. Arthur Bookman, M.D., New York.

Heart Block Associated with High Blood Pressure. John H. Musser, Jr., M.D., Philadelphia.

Studies in the Variations of the Tonus of the Gastric Musculature in Health and Disease. Burrill B. Crohn, M.D., and Abraham O. Wilensky, M.D., New York.

AUGUST, 1917. NUMBER 2

An Error in the Electrocardiogram Arising in the Application of the Electrodes. Harold E. B. Pardee, M.D., New York.

Studies in Protein Intoxication. II. Blood Coagulation. Howard F. Shattuck, M.D., New York.

Emetin Diarrhea—Clinical and Experimental. A. E. Kilgore, M.D., and J. M. Liu, M.D., Shanghai, China.

Studies on the Oxidase Reaction of the Cells in Normal and Leukemic Blood. M. Rosenthal, M.D., New York.

Relation of Pellagra to Location of Domicile in Spartan Mills, S. C., and the Adjacent District. J. F. Siler, M.D., P. E. Garrison, M.D., and W. J. MacNeal, M.D., New York.

SEPTEMBER, 1917. NUMBER 3

The Etiologic Agent of Rat Bite Disease. Preliminary Report. J. Kitagawa, M.D., and T. Mukoyama, M.D., Nagoya, Japan.

The Salicylates. VII. Salicyl Edema. P. J. Hanzlik, M.D., R.W. Scott, M.D., and J. L. Reverall, M.D., Cleveland.

A Study of Poliomyelitis. Report of the Work of the Meningitis Division of the Research Laboratory in the 1916 Epidemic. Josephine B. Neal, M.D., Harry L. Arnstein, M.D., and Associates, New York.

Further Studies with the Schick Test. Abraham Zingher, M.D., New York.

The Effect of Undernutrition on Muscular Force. A Study of the Influence of Low Diets, or the Allen Method of Treatment, on the Physical Vigor of Diabetics. John R. Williams, M.D., Rochester, N. Y.

Auricular Flutter. A Consideration of Some Problems Arising in the Study of a Case and of the Literature. James D. Heard, M.D., Pittsburgh, and Arthur K. Strauss, S.B., M.D., St. Louis.

Clinical Studies on the Respiration. III. A Mechanical Factor in the Production of Dyspnea in Patients with Cardiac Disease. Francis W. Peabody, M.D., Boston.

Clinical Studies on the Respiration. IV. The Vital Capacity of the Lungs and Its Relation to Dyspnea. Francis W. Peabody, M.D., and John A. Wentworth, M.D., Boston.

Clinical Studies on the Respiration. V. The Basal Metabolism and the Minute-Volume of the Respiration of Patients with Cardiac Disease. Francis W. Peabody, M.D., John A. Wentworth, M.D., and Bertha I. Barber, Boston.

Book Reviews:

A Monograph on the Epidemic of Poliomyelitis (Infantile Paralysis) in New York City in 1916.

The Diagnosis and Treatment of Myocardial Functions, with Special Reference to the Use of Graphic Methods. By L. Stuart Hart, A.M., M.D.

CONTENTS OF VOLUME XXI

JANUARY, 1918, NUMBER 1

PAGE

THE VALUE OF THE ATROPIN TEST IN THE DIAGNOSIS OF TYPHOID FEVER. EDWARD H. MASON, M.D., MONTREAL, QUEBEC 1

FACTORS IN RESISTANCE TO TUBERCULOSIS. WILLIAM F. PETERSEN, M.D., CHICAGO 14

LYPODYSTROPHIA PROGRESSIVA. IRVING J. SPEAR, M.D., BALTIMORE 39

THE EFFECT OF VARIOUS NEUTRAL SOLUTIONS ON GASTRIC DISCHARGE, GASTRIC SECRETION AND DUODENAL REGURGITATION. W. E. MORSE, A.B., M.D., CHICAGO 48

A SIMPLE TECHNIC FOR THE DEMONSTRATION OF A PHAGOCYTIC MONONUCLEAR CELL IN PERIPHERAL BLOOD. FIRST REPORT OF STUDIES ON THE MONONUCLEAR CELLS OF THE BLOOD. F. A. MCJUNKIN, M.D., MILWAUKEE 59

CALCIFICATION IN THE PINEAL GLAND. ERNST P. BOAS, M.D., AND THOMAS SCHOLZ, M.D., NEW YORK 66

ANATOMIC OBSERVATIONS CONCERNING THE MECHANISM OF BILE RESORPTION IN JAUNDICE. HORST OERTEL, M.D., MONTREAL, QUEBEC 73

STUDIES ON THE METABOLISM IN GOUT. J. A. WENTWORTH, M.D., AND C. W. MCCLURE, M.D., BOSTON 84

THE EFFECT OF DIET ON BLOOD SUGAR IN DIABETES MELLITUS. HERMAN O. MOSENTHAL, M.D., SAMUEL W. CLAUSEN, M.D., AND ALMA HILLER, M.D., BALTIMORE 93

STIMULATION OF THE RESPIRATION BY SODIUM CYANID AND ITS CLINICAL APPLICATION. A. S. LOEVENHART, M.D., W. F. LORENZ, M.D., H. G. MARTIN, M.D., AND J. Y. MALONE, M.D., MADISON, WIS 109

THE INFLUENCE OF LARGE DOSES OF THYROID EXTRACT ON THE TOTAL METABOLISM AND HEART IN A CASE OF HEART-BLOCK. J. C. AUB, M.D., AND N. S. STERN, M.D., BOSTON 130

EXTENSIVE CALCIFICATION OF THE LUNGS AS A DISTINCT DISEASE. FRANCIS HARBITZ, M.D., CHRISTIANIA, NORWAY 139

AURICULAR FLUTTER. JOHN M. BLACKFORD, M.D., SEATTLE, AND FRED A. WILLIUS, M.D., ROCHESTER, MINN 147

HEART-BLOCK. I. TWO CASES OF COMPLETE HEART-BLOCK SHOWING UNUSUAL FEATURES. FRANK N. WILSON, M.D., AND G. CANBY ROBINSON, M.D., ST. LOUIS 166

THE RATE OF ABSORPTION AND EXCRETION OF THE IODIDS OF STRONTIUM, SODIUM AND POTASSIUM. E. J. KRAHULIK, M.D., OMAHA, AND J. D. PILCHER, M.D., CLEVELAND 176

327338

FEBRUARY, 1918. NUMBER 2

PAGE

HEART BLOCK. II. TRANSIENT COMPLETE HEART BLOCK WITH NUMEROUS STOKES-ADAMS ATTACKS FRANK N. WILSON, M.D., AND G. CANBY ROBINSON, M.D., ST. LOUIS 181

THE ENDOCRINE ORIGIN OF MUSCULAR DYSTROPHY. N. W. JANNEY, M.D., S. P. GOODHART, M.D., AND V. I. ISAACSON, B.S., NEW YORK 188

STUDIES IN ACUTE NEPHRITIS. EDWARD H. MASON, M.D., MONTREAL, QUE. ... 216

A PAPILLARY CARCINOMA OF THE KIDNEY WITH METASTASIS IN THE BRAIN. EDWIN F. HIRSCH, M.D., CHICAGO 231

THE RELATIONSHIP OF THE TOXIC LYMPHOID HYPERPLASIAS TO LYMPHO-SARCOMA AND ALLIED DISEASES. DOUGLAS SYMMERS, M.D., NEW YORK .. 237

CHEMICAL CHANGES IN THE BLOOD AND URINE IN PROGRESSIVE MUSCULAR DYSTROPHY, PROGRESSIVE MUSCULAR ATROPHY AND MYASTHENIA GRAVIS. F. H. MCCRUDDEN, M.D., AND C. S. SARGENT, S.B., BOSTON 252

THE NATURE OF THE PATHOLOGIC PROCESS IN PROGRESSIVE MUSCULAR DYSTROPHY. F. H. MCCRUDDEN, M.D., BOSTON 256

THE EFFECT OF THYROID SECRETION ON THE EXCITABILITY OF THE ENDINGS OF THE CARDIAC VAGUS. ROBERT L. LEVY, M.D., BALTIMORE 263

THE MAINTENANCE DIET IN DIABETES MELLITUS AS DETERMINED BY THE NITROGEN EQUILIBRIUM. HERMAN O. MOSENTHAL, M.D., AND SAMUEL W. CLAUSEN, M.D., BALTIMORE 269

THE DISTRIBUTION OF BILE IN CERTAIN TYPES OF JAUNDICE. M. A. BLANKENHORN, M.D., CLEVELAND 282

EXPERIMENTAL INTESTINAL OBSTRUCTION. FRANK L. SOUTH, M.S., M.D., AND LEO J. HARDT, M.S., M.D., CHICAGO 292

MARCH, 1918. NUMBER 3

PAGE

A NOTE REGARDING MYIASIS, ESPECIALLY THAT DUE TO SYRPHID LARVAE. MAURICE C. HALL, PH.D., DETROIT 309

A COMPARISON OF THE FUNCTIONAL AND ANATOMIC FINDINGS IN A SERIES OF CASES OF RENAL DISEASE. A STENGEL, M.D., J. H. AUSTIN, M.D., AND L. JONAS, M.D., PHILADELPHIA 313

THE RELATIONSHIP OF THE SO-CALLED IDIOPATHIC CARDIOPATHY TO EXOPHTHALMIC GOITER. D. SYMMERS, M.D., NEW YORK 337

THE EFFECT OF DIURETICS ON THE GENERAL BLOOD PRESSURE IN ANIMALS WITH CONSTRICTION OF THE RENAL ARTERIES. E. W. BRIDGMAN, M.D., BALTIMORE, AND K. HIROSE, M.D., OKAYAMA, JAPAN 351

CONTRIBUTION TO THE PHYSIOLOGY OF THE STOMACH. XLVI. GASTRIC SECRETION DURING FEVER. J. MEYER, M.S., M.D., S. J. COHEN, S.B., AND A. J. CARLSON, PH.D., CHICAGO 354

INFLUENCES OF EXTRARENAL FACTORS ON THE RENAL FUNCTIONAL TEST MEAL. W. G. LYLE, M.D., AND H. SHARLIT, M.D., NEW YORK 366

A STUDY OF PAROXYSMAL TACHYCARDIA WITH ESPECIAL REFERENCE TO TACHYCARDIA OF VENTRICULAR ORIGIN. W. T. VAUGHAN, M.D., BOSTON 381

PHARMACODYNAMIC EXAMINATION OF THE VEGETATIVE NERVOUS SYSTEM IN TYPHOID FEVER: A CONTRIBUTION TO THE PROBLEM OF BRADYCARDIA. I. MATSUO, M.D., AND J. MURAKAMI, M.D., KIOTO, JAPAN 399

THE ACTION OF TYRAMIN ON THE CIRCULATION OF MAN. A. W. HEWLETT, M.D., SAN FRANCISCO 411

OBSERVATIONS REGARDING THE LOSS OF WATER VAPOR THROUGH THE SKIN OF INFANTS. W. B. MCCLURE, M.D., AND L. W. SAUER, M.D., CHICAGO 428

APRIL, 1918. NUMBER 4

PAGE

THE SUPERIORITY OF INOCULATION WITH MIXED TRIPLE VACCINE (B. TYPHOSUS, B. PARATYPHOSUS A, AND B. PARATYPHOSUS B) OVER SUCCESSIVE VACCINATIONS WITH THE SINGLE VACCINES, AS SHOWN BY AGGLUTININ CURVES IN MEN AND RABBITS. WILBURT C. DAVISON, M.D., PHILADELPHIA 437

A STUDY OF THE METABOLISM OF ASTHMA. EDWIN ZUGSMITH, M.D., PITTSBURGH, AND MAX KAHN, M.D., PH.D., NEW YORK 510

CONGLOMERATE TUBERCLE AND COMBINED DEGENERATION OF THE CORD AS COMPLICATIONS OF VISCERAL TUBERCULOSIS. PETER BASSOE, M.D., CHICAGO 519

THE PITUITARY GLAND IN EPILEPTICS. THE CONFORMATION OF THE SELLA TURCICA. SECOND PAPER. J. F. MUNSON, M.D., SONYEA, N. Y. 531

THE INTRAVENOUS SERUM TREATMENT OF EPIDEMIC CEREBROSPINAL MENINGITIS. MAJOR W. W. HERRICK, M.D., CAMP JACKSON, S. C. 541

BOOK REVIEW: TEXTBOOK OF THE PRACTICE OF MEDICINE, BY JAMES M. ANDERS, M. D. 564

MAY, 1918. NUMBER 5

PAGE

EXPERIMENTS ON THE VASOCONSTRICTOR ACTION OF BLOOD SERUM. THEODORE C. JANEWAY, M.D., HENRY B. RICHARDSON, M.D., AND E. A. PARK, M.D., BALTIMORE 565

RELATION BETWEEN THE PLATELET COUNT OF HUMAN BLOOD AND ITS VASOCONSTRICTOR ACTION AFTER CLOTTING. K. HIROSE, M.D., OKAYAMA, JAPAN 604

CLINICAL CALORIMETRY. PAPER 26. THE EFFECT OF A SMALL BREAKFAST ON HEAT PRODUCTION. G. F. SODERSTROM, DAVID P. BARR, M.D., AND EUGENE F. DU BOIS, M.D., NEW YORK 613

CLINICAL CALORIMETRY. PAPER 27. METABOLISM OF BOYS TWELVE AND FOURTEEN YEARS OLD. WILLIAM H. OLMSTEAD, M.D., DAVID P. BARR, M.D., AND EUGENE F. DU BOIS, M.D. (WITH THE TECHNICAL ASSISTANCE OF G. F. SODESTROM), NEW YORK 621

CLINICAL CALORIMETRY. PAPER 28. THE METABOLISM IN MALARIAL FEVER. DAVID P. BARR, M.D., AND EUGENE F. DU BOIS, M.D. (WITH THE TECHNICAL ASSISTANCE OF G. F. SODERSTROM), NEW YORK 627

A FURTHER STUDY OF ETHYLHYDROCUPREIN (OPTOCHIN) IN THE TREATMENT OF ACUTE LOBAR PNEUMONIA. HENRY F. MOORE, M.D., B.CH., AND ALAN M. CHESNEY, M.D., NEW YORK 659

CIRCULATORY REACTIONS TO EXERCISE DURING CONVALESCENCE FROM INFECTIOUS DISEASE. HUBERT MANN, M.D., NEW YORK 682

THE OCCURRENCE OF MITOCHONDRIA IN THE RED BLOOD CORPUSCLES DURING EXPERIMENTAL ANEMIAS. CLARENCE OLDS SAPPINGTON, A.B., SAN FRANCISCO 695

CONTENTS OF VOLUME XXI

JUNE, 1918. NUMBER 6

PAGE

RENAL GLYCOSURIA. A. H. BEARD, M.D., AND FLOYD GRAVE, M.D., MINNEAPOLIS 705

SALT METABOLISM IN DIABETES MELLITUS. A. H. BEARD, M.D., MINNEAPOLIS 716

THE EGGLESTON METHOD OF ADMINISTERING DIGITALIS (WITH SOME NOTES ON DIGITALIS LUTEA). S. MARX WHITE, M.D., AND R. EDWIN MORRIS, M.D., MINNEAPOLIS 740

ANTIGEN-ANTIBODY BALANCE IN LOBAR PNEUMONIA. FRANCIS G. BLAKE, M.D., MINNEAPOLIS 779

BRAIN CHANGES ASSOCIATED WITH PERNICIOUS ANEMIA. HENRY W. WOLTMAN, M.D., MINNEAPOLIS..... 791

BOOK NOTICE 844

INDEX TO VOLUME XXI..... 845

Theodore Caldwell Janeway, M.D.

1872-1917

Major, M.R.C., U. S. Army

THEODORE CALDWELL JANEWAY, M.D., a member of the editorial board of The Archives of Internal Medicine since 1908, died of pneumonia, Dec. 27, 1917, in Baltimore, aged 45 years. Dr. Janeway was born in New York City, Nov. 2, 1872, a son of Dr. Edward Gamaliel Janeway, the well-known diagnostician and consulting physician of New York, who died in 1911, and of Frances Strong Rogers Janeway. He married Miss Eleanor C. Alderson of Overbrook, Pa., Sept. 27, 1898, and is survived by his wife, two sons, Edward and Charles, and three daughters, Nora, Agnes and Francesca Janeway.

Dr. Janeway graduated from the Sheffield Scientific School of Yale University in 1892, and from the College of Physicians and Surgeons of Columbia University in 1895. He was instructor of bacteriology in Columbia University, 1895-1896; an intern in St. Luke's Hospital in 1897; instructor and lecturer in the University and Bellevue Medical College, 1898-1906; associate in clinical medicine in the College of Physicians and Surgeons of Columbia University, 1907; professor of medicine, 1909; visiting physician to St. Luke's, the City and the Presbyterian hospitals of New York City; physician-in-chief of Johns Hopkins Hospital and professor of medicine in the Johns Hopkins University under the Welch fund, 1914. He became secretary of the Russell Sage Institute of Pathology in 1907, and was a member of the Board of Scientific Directors of the Rockefeller Institute for Medical Research since 1911.

Dr. Janeway was a Fellow of the American Medical Association, a member of the Association of American Physicians, and of the Society of Experimental Biology and Medicine. His work in the different branches of clinical medical investigation, notably on the subjects of blood pressure and diseases of metabolism and the cardiovascular changes in nephritis, was especially noteworthy. He was the author of "The Clinical Study of Blood Pressure," published in 1904, and of many periodical articles.

Dr. Janeway offered his services to the Medical Department of the Army immediately after the declaration of war by the United States.

and was assigned to active duty in the Surgeon-General's office at Washington with general direction of the Division of Internal Medicine. The splendid personnel of the internists in charge of internal medicine and cardiovascular-renal diseases in the cantonments and camps was obtained largely through his efforts with the cooperation of Major Warfield T. Longcope. Just previous to his death, Dr. Janeway had made a personal investigation of the outbreak of measles and pneumonia in some of the cantonments. In addition to his continuous work in the Surgeon-General's office, he conducted two clinics a week in Baltimore, and it seems likely that this severe drain on his strength and energy weakened his power of resistance.

Through his many scientific interests and connections, Dr. Janeway did much to advance the growth of medical science in this country. He was a man of lovable character, an energetic worker; and he gave himself wholeheartedly and freely to the many worth while undertakings to which he was called.

The Archives of Internal Medicine

Vol. XXI JANUARY, 1918 No. 1

THE VALUE OF THE ATROPIN TEST IN THE DIAGNOSIS OF TYPHOID FEVER*

EDWARD H. MASON, M.D.
MONTREAL, QUE.

With the recent publication of Marris'[1] article on the use of atropin in the diagnosis of the enteric group of infections, we decided to avail ourselves of the opportunity that the medical services of this hospital offered. Therefore, within the last few months we have carried out the test according to Marris' technic on 109 patients, sixty-three of them suffering from typhoid, or paratyphoid B infections, and forty-six nontyphoid cases. In all, 305 tests were performed. The technic adopted is practically the same as that recommended by Marris, except that in most of our tests we have used one-thirtieth in place of one-thirty-third grain of atropin sulphate. It is as follows:

On a fasting stomach the pulse rate is taken for ten consecutive minutes, while the patient rests quietly in bed. If the rate per minute remains practically constant, this is accepted as the average mean rate. Then one-thirtieth grain of atropin sulphate is injected hypodermically into the upper arm, after which the patient continues to remain quietly in the same position. After twenty minutes have elapsed the pulse rate is taken again and the counting is continued until the maximum rate per minute has been reached and it has definitely started to fall to a lower level. The difference between this high level and the mean of the ten consecutive minutes before the injection is taken as the release.

In most normal persons the pulse rate increases from twenty to forty beats per minute after one-thirtieth grain of atropin sulphate hypodermically. The increase is more marked in the earlier years of adult life, while after 50 it is not so great. The question of sex seems to play no important part in regard to the degree of release. Marris found this release to be so constant that he declared that an increase of only ten beats or less per minute was very suggestive that the patient was suffering from a typhoid or paratyphoid infection. Releases between ten and twenty he considered to be doubtful, needing to be confirmed by further observations. In our work we have taken a

* Submitted for publication July 24, 1917.
* From the Medical Clinic of the Royal Victoria Hospital, Montreal.
* I should like to acknowledge my appreciation of a grant from the James Cooper Fund of McGill University which made this work possible.

1. Marris, F. A.: Brit. Med. Jour., 1916, **2**, 717.

release of ten as the dividing line between a positive and a negative result. Also during the earlier part of our work, we started counting the pulse rate twenty-five minutes after the injection, but in a few cases the maximum release took place within that time, so a twenty-minute period was adopted. This has proved to be quite satisfactory.

In all, we have carried out 256 tests on sixty-three cases of typhoid or paratyphoid B infections, fifty-seven of them being on males and six on females. The dosage of the drug has been either one-thirtieth or one-thirty-third grain of atropin sulphate hypodermically, most of the tests being made with one-thirtieth grain. Fifty-six were cases of typhoid fever, the diagnosis being confirmed by blood culture, or by a Widal reaction in dilution above 1 in 40. Five of the remaining seven cases were infections due to *B. paratyphosus* B, while the remaining

TABLE 1.—RESULTS OF THE ATROPIN TEST IN SEVEN CASES SHOWING THE VARIABILITY IN TIME OF APPEARANCE OF A POSITIVE WIDAL REACTION

Case No.	Sex	Day of Disease	Release	Widal (Mac.)	Blood Culture
25537	♂	6 10	87-100 = 13 82- 88 = 6	5th day of disease, negative for B. typhosus	Positive for B. typhosus
25625	♂	9 13	77- 98 = 21 82- 88 = 6	8th day of disease, positive (1-80) for B. typhosus	Positive for B. typhosus
25662	♀	10 16	111-132 = 21 115-120 = 5	10th day of disease, positive (1-160) for B. typhosus	Positive for B. typhosus
25515	♂	5 10	94-110 = 16 86- 86 = 0	4th day of disease, negative for B. typhosus	Positive for B. typhosus
25521	♂	18 22	81-104 = 23 79- 86 = 7	18th day of disease, positive for B. typhosus	Positive for B. typhosus
25128	♂	11 15	98-116 = 18 95-100 = 5	15th day of disease, negative for B. typhosus	Positive for B. typhosus
25700	♀	9 15	106-122 = 16 114-122 = 8	8th day of disease, positive for B. typhosus (1-80)	Positive for B. typhosus

two ran a typical typhoid course, but at no time were we able to confirm our diagnosis by bacteriologic or by serologic methods. Out of the sixty-three cases, eleven of them failed to give a positive reaction, that is a release of ten or less. This is an exceedingly high percentage, but it may be partly accounted for by the fact that six of the eleven patients were given only one test. Further, three of the eleven were extremely toxic and restless at the time of the test, which undoubtedly increased the release, all of these three patients dying a few days later.

Only seven patients admitted showed a negative test before developing a positive one. As this point determines the appearance of the reaction in relation to the day of disease the results are given in full (Table 1). From the seven cases recorded in Table 1 it would seem that the time of appearance of a positive reaction varies considerably.

Thirty-five of our cases were admitted to the wards early enough so that the first test, if positive, would be of some value in determining the appearance of the reaction. The average of these thirty-five cases indicated that the reaction appeared on the eleventh day of disease, with

TABLE 2.—DATA CONCERNING ELEVEN CASES WHICH FAILED TO GIVE A POSITIVE REACTION TO THE ATROPIN TEST

Serial No.	Case No.	Sex	Age	Day of Disease	Release	Widal (Mac.)	Blood Culture	Remarks
1	25310	♂	32	6	99-116=17	Negative for B. typhosus (5th day of disease)	Negative for B. typhosus (5th day of disease)	Only 1 test diagnosis doubtful
2	25296	♂	32	11 25 31 42	60- 73=13 48- 65=17 57-101=44 82-100=18	Negative for B. typhosus (10th day of disease)	Positive for B. typhosus (10th day of disease)	
3	25284	♂	28	28	108-124=16	Negative for B. typhosus (28th day of disease)	Positive for B. typhosus (28th day of disease)	Died 9 days later; only one test made
4	25445	♂	18	11 19 27 31 35 38 41	99-126=27 88-100=12 66- 84=18 77- 92=15 73- 90=14 77- 90=13 72- 90=18	Negative for B. typhosus (9th day of disease)	Positive for B. typhosus (9th day of disease)	
5	25209	♂	33	10	94-110=16	Positive (1-20) for B. typhosus (9th day of disease)	Positive for B. typhosus (9th day of disease)	Died 10 days later; one test
6	25595	♂	18	15 20	86-104=18 80- 94=14	Positive for B. typhosus (15th day of disease)	Positive for B. typhosus (15th day of disease)	Died 29th day of disease
7	25096	♂	25	16	105-120=15	Positive (1-80) for B. typhosus (12th day of disease)	Negative.....	One test
8	24958	♂	30	29	82-114=32	Positive (1-80) for B. typhosus (9th day of disease)	Negative.....	One test
9	25601	♂	23	15 22 27	70-100=30 75- 92=17 96-120=24	Positive (1-80) for B. typhosus (18th day of disease)	Negative	
10	25119	♂	32	17	74- 88=14	Positive (1-80) for B. typhosus (14th day of disease)	Negative.....	One test
11	25653	♂	27	21 24 38 42	84-112=28 91-112=21 93-112=19 86-112=26	Positive (1-160) for B. typhosus (20th day of disease)	Negative	

extremes from the fourth to the twenty-second days. It must be remembered that in twenty-eight of these cases the reaction was positive with the first test, so it undoubtedly appears at a slightly earlier date. It has been of great interest to us to observe that in twelve of

these thirty-five cases the test was positive, with a negative Widal reaction and positive blood culture. Also in four cases both Widal reaction and blood culture were negative with positive atropin tests, the former becoming positive at subsequent dates. This would indicate that in a few cases the test might rival the blood culture as an early means of diagnosis.

The disappearance of the reaction in relation to the day of disease and to the temperature is important. In twenty-seven cases in which we were able to determine the former point the reaction averaged to disappear on the thirty-first day of disease. The extremes ranged from the fifteenth to the fifty-fourth days. As a rule, the temperature curve ranged between 98 to 100 F. when the reaction disappeared, and in a few cases it reappeared slightly preceding a relapse with a rise in temperature.

The eleven cases with their points of interest that failed to give a positive reaction (release of ten or less) during some period of their hospital stay are recorded in Table 2.

We have had no experience with the use of the test in patients who have had typhoid vaccine. Marris gave evidence to show that the test was positive within four weeks of such vaccination, which would make it of value only after that interval had expired.

In order to control the work, forty-nine tests were carried out on forty-six ward patients suffering from a variety of clinical conditions. Thirty-six of these patients were males, and ten were females. The dosage in all cases except one was one-thirtieth or one-thirty-third grain, and in that case it was one-seventy-fifth grain, as the patient was a boy of 13 years. The releases varied from one to fifty-four, the average release for all cases being 21.5 beats per minute. By sex the extremes are:

Males (nonfebrile)	30 cases;	31 tests;	11 to 45
Males (febrile)	6 cases;	6 tests;	14 to 30
Females (nonfebrile)	7 cases;	9 tests;	1 to 54
Females (febrile)	3 cases;	3 tests;	13 to 50

Average release (all cases nontyphoid)	21.5
Average release males (nonfebrile)	23.6
Average release males (febrile)	18.8
Average release females (nonfebrile)	16.5
Average release females (febrile)	27.0

The foregoing figures show how variable the release may be in people who are not suffering from the enteric group infections. Three females gave a release of ten or less, a positive reaction. One, a case of acute bronchitis, on two occasions gave releases of one and eight, respectively. The blood failed to agglutinate *B. typhosus* or *B. paratyphosus* A or B.

The second case was one of tuberculous meningitis in a woman, aged 60, who also, on two occasions, gave releases of four and nine. This may be explained by the well known hyperactive vagus which is present in certain cases of tuberculous meningitis.

The third, a case of diabetes mellitus in a woman of 50, gave a release of ten. In none of these three cases was there a previous history of typhoid fever or of typhoid vaccination.

In the series of nontyphoid men there were four cases that each gave a release of eleven. One was a patient who had vagotonia and who at the same time was taking 30 minims of tincture of belladonna per day. He showed neither pupillary changes nor a dry mouth. The other three were cases of gout, chronic arthritis, and multiple neuritis, respectively. In all, pupillary changes were definite.

Thus, when the five tests in the three females that released only ten or less are excluded, the total average release is 23.9; for males alone 22.8, and for females alone 32.8. This might indicate that females are more sensitive than males to one-thirtieth grain of atropin. The types of cases covered in this group can be seen by the following diagnoses:

AFEBRILE

Gout	Cerebral hemorrhage
Diabetes mellitus	Peripheral neuritis
Acute nephritis	Myalgia
Chronic diffuse nephritis	Vagotonia
Chronic arthritis, infectious	Cerebrospinal syphilis
Gonorrheal arthritis	Tabes dorsalis
Acute bronchitis	Splenomyelogenous leukemia
Chronic bronchitis	Chronic malaria
Pleurisy with effusion	Chronic appendicitis
Chronic pulmonary tuberculosis	Duodenal ulcer
Tuberculous meningitis	Cerebral concussion
Myocarditis	Sarcoma lumbar vertebrae
Thoracic aneurysm	

FEBRILE

Acute nephritis	Acute endocarditis
Acute bronchitis	Acute infectious arthritis
Pulmonary tuberculosis	Chronic infectious arthritis

On the nontyphoid group we have also worked out the minute that the high level of release first appears after the hypodermic injection of atropin. We find it to vary from the fifteenth to the fifty-second minute. The results are:

Average of all cases	33.5 minute
Males (nonfebrile)	31.6 minute
Males (febrile)	34.0 minute
Females (nonfebrile)	28.7 minute
Females (febrile)	32.0 minute

The foregoing results would indicate that the release appears a little sooner in women than in men, and that in both sexes the non-

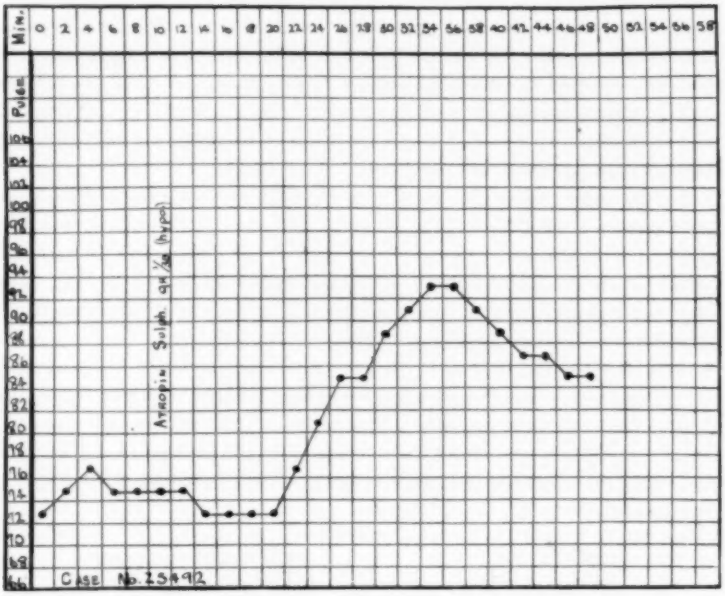


Chart 1

EXPLANATION OF CHARTS

The first three charts represent the complete pulse rate curve after the injection of one-thirtieth grain of atropin sulphate in three nontyphoid patients. The scales explain themselves. Chart 1 is taken in a case of diabetes mellitus and shows very clearly the release of 18 beats which took place, the high level of release being reached twenty-four minutes after the drug was given. The slight slowing in rate which was maintained for 8 beats is of very common occurrence, due we believe to a hyperactive vagus before the partial paralysis takes place.

Charts 2 and 3 show similar curves in cases of pleurisy with effusion and in pulmonary tuberculosis respectively, giving releases of thirty-two and thirty-one. Note the slowed rate after the hypodermic for twelve beats in Chart 2.

Charts 4 and 5 represent curves from cases of typhoid fever in the thirteenth and fourth days of disease. The releases of two and of six make the reaction positive.

Charts 6, 7 and 8, demonstrate the presence of the reaction throughout the course of three cases of typhoid fever, which diagnoses were confirmed by laboratory examinations. The releases are represented in black and are read from the pulse scale at the extreme left. The finest ruling represents two beats and the darker ones ten, the dividing line between a positive and a negative result. The charts also show the relation between the reaction, temperature curve, and day of disease. The facts of interest in each case are given under the charts.

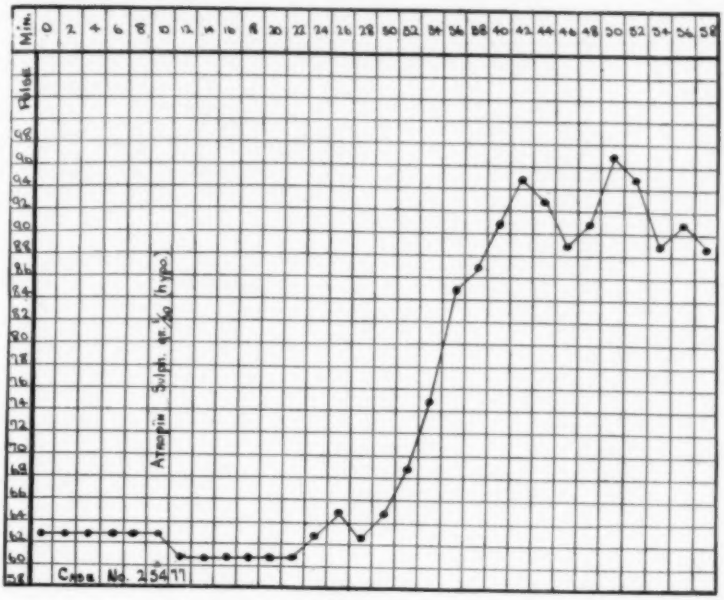


Chart 2

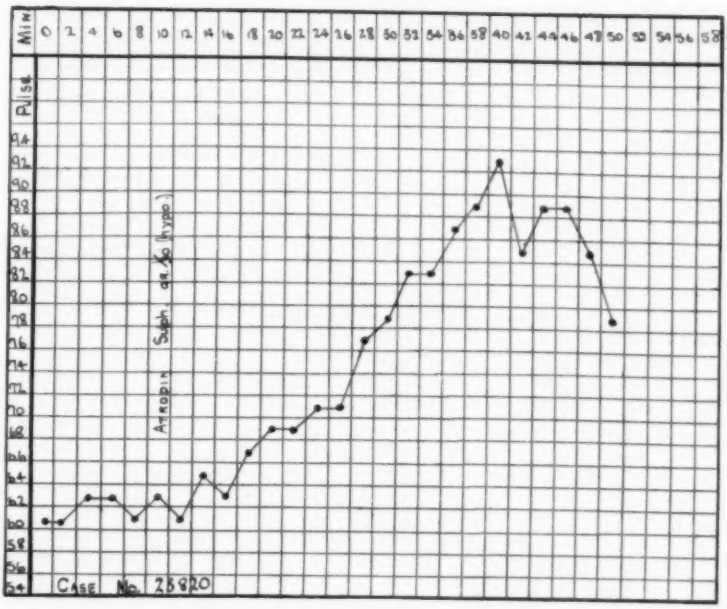


Chart 3

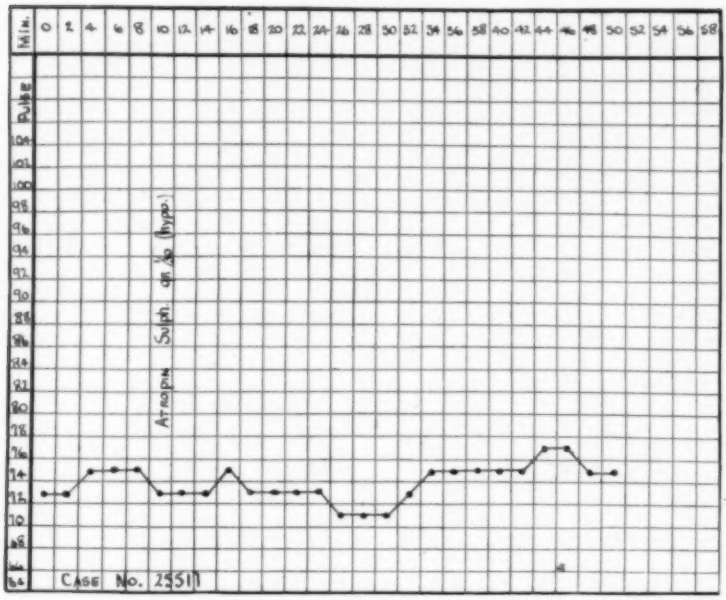


Chart 4

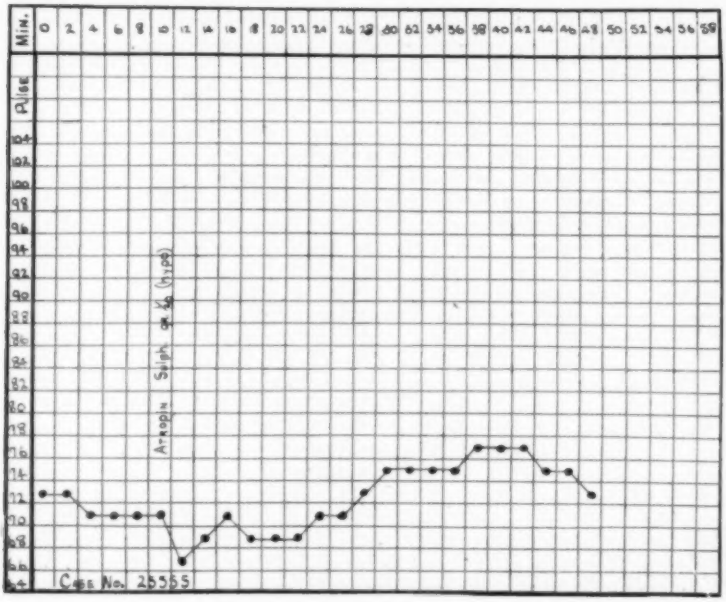


Chart 5

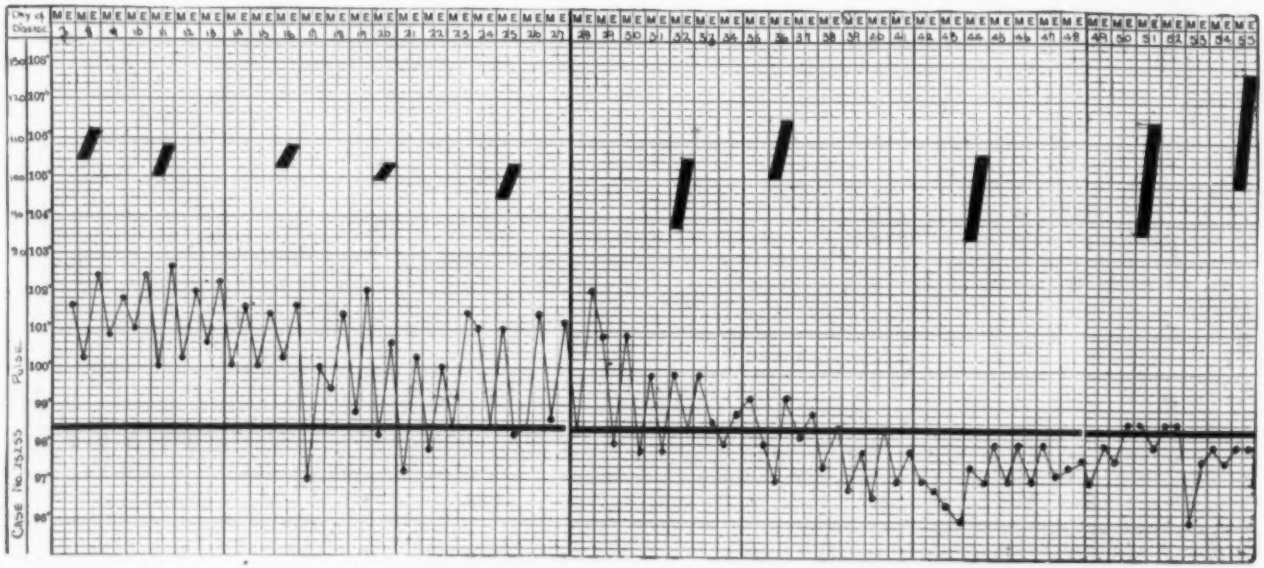


Chart 6.—Man, aged 38, colored. Diagnosis, typhoid fever; admitted on the seventh day of the disease; Widal reaction positive (1:680); blood culture positive. Atropin tests: Dose one-thirtieth grain atropin sulphate (hypodermically).

TABLE 3.—Tabulated Summary of the Data Recorded on Chart 6

Number	Day of Disease	Release	Minute of Appearance of Maximum Release
1	8	102-111 = 9	33
2	11	100-108 = 8	35
3	16	102-108 = 6	39
4	20	99-103 = 4	24
5	25	99-108 = 11	38
6	32	87-105 = 18	36
7	36	100-115 = 15	33
8	44	82-106 = 24	31
9	51	86-115 = 29	25
10	55	98-128 = 30	25

TABLE 4.—Summarized Record of the Results Illustrated in Chart 7

Number	Day of Disease	Release	Minute of Appearance of Maximum Release
1	8	92- 96 = 4	22
2	13	73- 76 = 3	30
3	16	83- 90 = 7	27
4	21	64- 76 = 12	29
5	25	57- 64 = 7	29
6	29	66- 78 = 12	35
7	32	65- 76 = 11	26
8	37	70- 80 = 10	24
9	44	77-106 = 29	22
10	48	65- 92 = 27	42

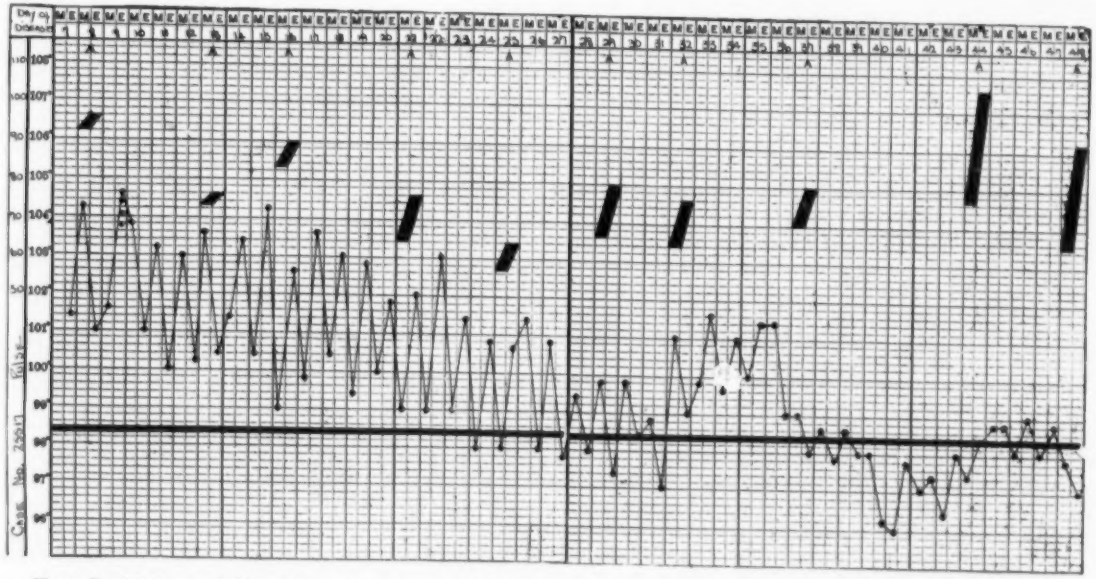


Chart 7.—Male, aged 20, white. Diagnosis, typhoid fever; admitted on the seventh day of the disease; Widal reaction negative; blood culture negative; Widal positive at a later date. Atropin tests: Dose one-thirtieth grain of atropin sulphate (hypodermically).

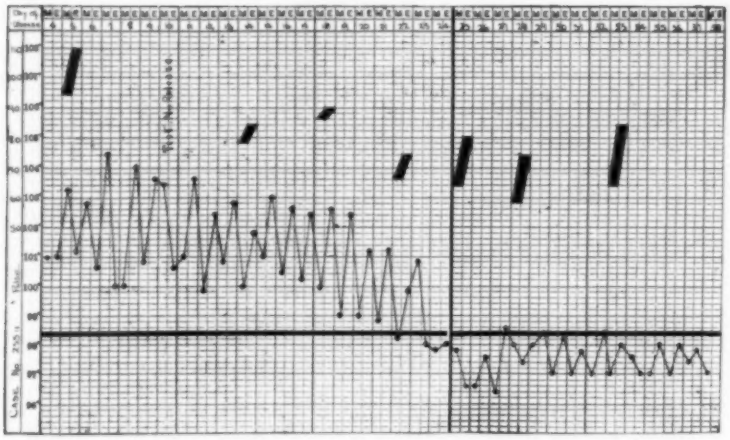


Chart 8.—Man, aged 25. Diagnosis, typhoid fever; admitted on the fourth day of the disease; Widal reaction negative; blood culture positive. Atropin tests: Dose one-thirtieth grain atropin sulphate (hypodermically).

TABLE 5.—Results of Atropin Tests Summarized from the Findings Recorded in Chart 8

Number	Day of Disease	Release	Minute of Appearance of Maximum Release
1	5	94-110 = 16	32
2	10	86- 86 = 0	0
3	14	78- 84 = 6	26
4	18	86- 90 = 4	36
5	22	66- 74 = 8	34
6	26	64- 80 = 16	22
7	29	58- 74 = 16	26
8	34	65- 84 = 19	31

febrile cases release more quickly than the febrile ones. This early release was very evident with our women who had typhoid fever, and largely on that account did we adopt a twenty-minute interval instead of a twenty-five minute one before counting the pulse after the hypodermic injection.

The subjective symptoms after one-thirtieth grain of atropin sulphate hypodermically in the patients having typhoid fever were almost nil, and in no case that gave a positive release did we find any pupillary changes. In the nontyphoid group most of the patients had dilated pupils and dry mouths for a short time after the test. Otherwise no bad effects were noted.

SUMMARY

Three hundred and six atropin tests were performed on 109 patients, 63 typhoid patients or paratyphoid B patients, and 46 on nontyphoid patients. Eleven of the typhoid group cases failed to give the reaction. This has been discussed previously.

The reaction becomes positive at about the tenth and disappears at about the thirty-first days of disease.

In the nontyphoid group three cases gave a positive reaction. We offer no explanation of these findings.

In the diagnosis of fevers of the enteric group, we believe the test to be of great value, and in many cases undoubtedly precedes the Widal reaction.

As a means of diagnosing the syndrome termed vagotonia we would suggest the use of atropin in the above manner.

FACTORS IN RESISTANCE TO TUBERCULOSIS*

WILLIAM F. PETERSEN, M.D.
CHICAGO

When the literature dealing with the tuberculin reaction and immunity phenomena in general in relation to tuberculosis is surveyed it is rather surprising to note the decided skepticism which has found expression in recent times concerning the more or less current immunologic conception of the mechanism of the tuberculin reaction. Kraus, Landmann, Löwenstein and Volk, Aronson, Bessau, to mention only a few, have published observations which have led them to doubt the adequacy of the antigen-antibody conception. The fact that up to the present the major part of experimental work in tuberculosis has been along strictly immunologic lines, without apparently resulting in any substantial advance in our knowledge of the disease process or its therapy, is possibly the underlying reason that this skepticism has developed, for as yet no other adequate explanation has been put forward by the various workers which might serve as a basis for the diverging views. The existing confusion is due in part to the fact that immunologic ideas and terms have been maintained and used to express phenomena concerned with anaphylactic reactions as well as certain ferment changes; in part it is due to the fact that a large share of the literature is clinical in character and the observers have reiterated fallacious immunologic theories until the repetition has of itself seemingly carried the weight of uncontrovertible authority; perhaps, too, the fact that the effort is made to explain the skin reaction (von Pirquet) and the general reaction (subcutaneous) on one and the same basis, while as a matter of fact they are dissimilar in many important respects, has contributed in no small measure.

The whole trend of the study of tuberculosis has focused about the resistance to an established infection. The fundamental ideas concerning the factors involved in the establishment of the infection itself have been largely accepted, while the forces that protect the individual against infection are, from a practical standpoint, so largely social and economic that less interest has been attached to them from the experimental side. Until recent times, the idea that resistance to infection

* Submitted for publication June 25, 1917.

* From the Medical Clinic of Joseph L. Miller at the Cook County Hospital, and the Laboratory of Physiologic Chemistry, College of Medicine University of Illinois.

need not depend wholly on specific immune bodies has been largely ignored in experimental work, although the clinician was often compelled to rely solely on this uncertain factor in his treatment of the disease.

The data presented in this paper represent observations along experimental lines not immunologic in the usual sense, but having to do rather with some of these nonspecific reactions on the part of the host. If presented at all, it is with the hope that, however inadequate, they will be of interest in the interpretation of clinical problems as yet obscure.

For the time being it may be well to keep in mind certain facts accepted by recent workers as fundamental to the discussion to follow. These are the following: (1) the cutaneous reaction appears to be specific and is related to a definite sensitization; the resistance to this reaction need not be specific; (2) the subcutaneous reaction has no relation whatever to antibody concentration of either serum or cells; when the disease focus (tubercle) is removed the reaction becomes negative; the reaction can be elicited by nonspecific methods; (3) tuberculin treatment has no specific significance and its beneficial effects have no relation to an active immunization. The actual demonstration of an increase in antibody concentration in tuberculosis is not necessarily associated with favorable clinical results; recovery does not depend on the presence of specific antibodies.

CASEATION

The tubercle bacillus differs from most other organisms in its abundant fat and wax content, some 35 to 45 per cent. of the total dry weight consisting of lipoid bodies, including waxes, fatty acids and neutral fats. When such bacteria undergo disintegration in the tissues this relatively resistant waxy material remains in situ for a considerable period of time. It happens that these lipoids, being unsaturated, provided their state of dispersion be great enough, act as antiferments against tryptic and leukoproteolytic ferments. This property of checking proteolysis depends, therefore, on both a chemical configuration — the number of unsaturated carbon bonds available, and on a physical basis — the ultimate state of division or dispersion. These fat and wax bodies probably do not exist free as such either in the living bacilli or in the infected tissues after the death of the organisms, but most probably as an intimate protein-lipoid combination, that is, a combination in the physical rather than in the chemical sense.

As the tubercle bacillus finds lodgment and multiplies in the tissues it entails the destruction of a certain number of tissue cells. This is brought about through the excretion of toxic metabolic products, or

possibly through the medium of extracellular bacterial ferments. Under ordinary pathologic conditions, tissue death is followed by autolysis and the removal of the fluid end-products through the vascular channels. It is apparent that this does not take place in caseation; autolysis is in some way prevented and the necrotic debris accumulates. It is true that the cellular reaction about the tubercle does not include polymorphonuclear leukocytes, which, because of their abundant proteolytic ferment content, liberated when they disintegrate, hasten autolytic processes; instead we find lymphocytes, the lipase carrying cells. But tissue autolysis does not depend on the presence of polymorphonuclear leukocytes, and the absence of autolysis in caseous foci indicates some inhibitory factor. The explanation for this is found in the presence of the unsaturated lipoids derived from the tubercle bacilli. These are able to bind and inhibit the action of any autolytic ferments that may be present and thereby prevent autolysis. That this is actually the case is readily demonstrated by the fact (*a*) that caseous material when extracted by the lipoid solvents will become digestible by trypsin; (*b*) that the lipoids extracted will act as antiferments and will, when injected into normal tissues, cause typical caseous foci. Of equal importance is the fact that when caseous material is treated with iodin, which presumably saturates some of the unsaturated carbon bonds, tryptic digestion can take place.

In general terms, we can consider the tubercle as a necrotic mass consisting of native proteins and of lipoids derived partly from the cells and partly from the tubercle bacilli, together with some of the higher and less diffusible protein split products. Bounding this necrotic mass we have to consider connective tissue, endothelial cells, lymphocytes and a few polymorphonuclear leukocytes; the whole permeated with the tissue fluid, which in man contains only a moderate amount of lipase, some protease and peptidase, and a large amount of antiferment, the latter in an amount quite sufficient to overbalance any ordinary extracellular proteolytic activity. The quiescent tubercle represents a balance between the digestive and digestion inhibitory forces; that is, it serves as a potential source of toxic split products derived from the necrotic material, potential rather than actual, because the active autolysis and removal into the circulation of the products of autolysis is prevented by the antiferment. Any factor that will alter the conditions of this delicate balance so that autolysis can occur will bring about a toxic reaction, that is, a tuberculin reaction. This may be brought about if we increase the ferments of the serum, or decrease the antiferment of the necrotic focus or of the serum. It is apparent that such an alteration need have no relation to specificity.

THE RELATIONS OF THE SERUM ALTERATIONS OF PREGNANCY AND MENSTRUATION ON THE TUBERCULOUS FOCUS

During the past few years we have become familiar with certain of the serum changes that take place during pregnancy. With the aid of this knowledge we can follow the changes that occur in the tuberculous process as a result of these definitely understood serum alterations of pregnancy, in order to throw some light on the reactions involved.

One of the first things that occurs after the onset of the pregnancy is a reduction of the blood and tissue lipases, the fat splitting ferments. We have, as yet, no knowledge as to the source of these ferments, although there is evidence (Stuber) that points to glands of internal secretion as involved in the regulation of the production. As a sequel of this lipase reduction an accumulation of fats and lipoids takes place in the blood stream. This change in the blood lipoids is both quantitative and qualitative, as determined by numerous analyses.[1] Inasmuch as the serum antiferment also consists of these lipoids, those that are unsaturated, we can expect an increase in the antiferment titer of the serum.[2] This increase is so constant in pregnancy that the test for this antiferment rise has been repeatedly advocated as a test for pregnancy. The increase comes on early, reaches the maximum at the time of labor and then rapidly — from five to seven days — returns to a normal level (Chart 1).

This antiferment rise is probably of decided physiologic importance in raising the threshold of protein metabolism. In 1915, Jobling[3] showed that the rate of nitrogen excretion in the starving rabbit was almost inversely proportional to the level of the antiferment titer; that is, if the antiferment was high the rate of protein metabolism was low; if the antiferment was reduced, on the other hand, much nitrogen was excreted. Wilson, in a paper published last year,[4] describes the metabolism of the pregnant woman in a way that leads one to believe that the relation that Jobling noticed in the rabbit holds good for the pregnant woman, and for a like reason, that is, the increase in antiferment brings about a positive nitrogen balance.

In the particular case charted (Chart 1, after Wilson) a total storage of about 420 gm. of nitrogen took place in the five-months' period of observation. Even if the nitrogen of the birth products

1. Herrmann, E., and Neumann, J.: Wien. klin. Wchnschr., 1912, **25,** 1557. Fränkel, S.: Wien. med. Wchnschr., 1913, **63,** 2198.

2. Franz, R.: Arch. f. Gynäk., 1914, **102,** 79. V. Graff, E., and V. Zubrzycki, J.: Ztschr. f. Geburtsh u. Gynäk., 1912, **72,** 303. Gammeltoft, S. A.: Gynäk. Rundschau, 1913, **7,** 543.

3. Jobling, J. W., and Petersen, W. F.: Ztschr. f. Immunitätsforsch., Orig., 1915, **24,** 219.

4. Wilson, Karl: Bull. Johns Hopkins Hosp., 1916, **27,** 121.

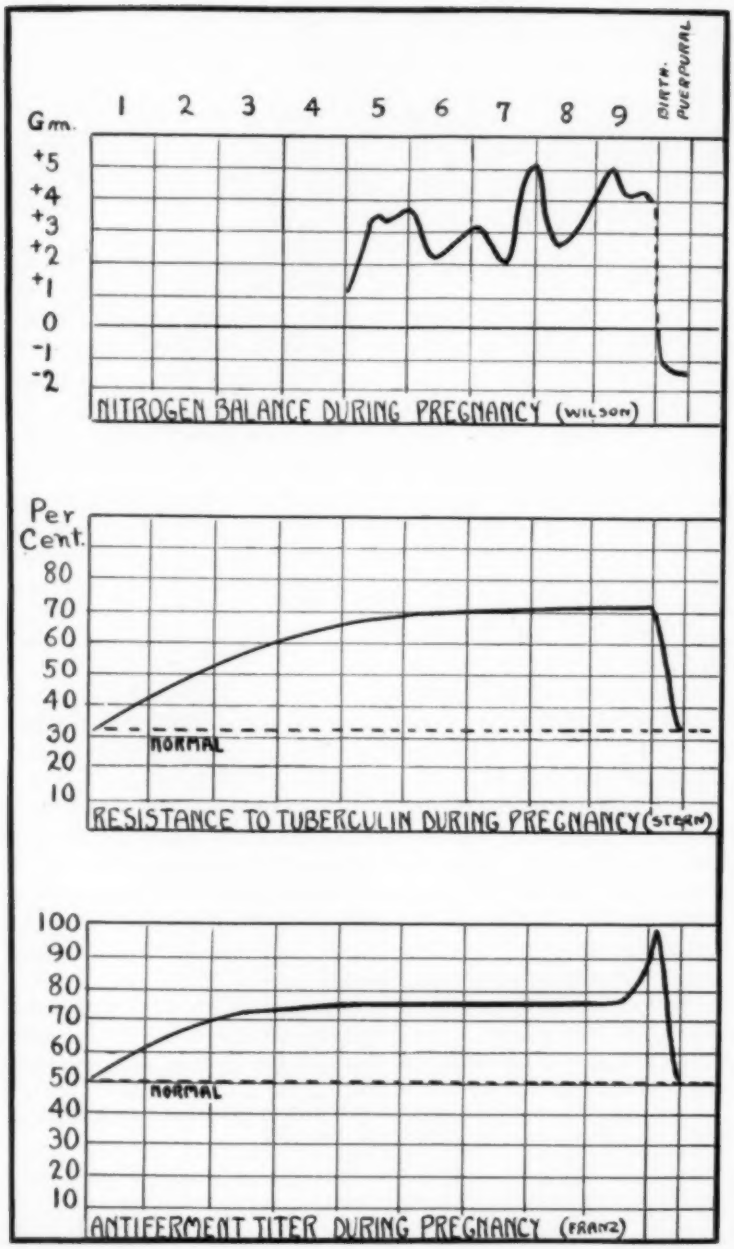


Chart 1.—Relation of the antiferment during pregnancy to the nitrogen metabolism and resistance to tuberculin.

and that estimated for the hyperplasia of the uterus and breasts is subtracted, Wilson considers that fully 285 gm. of nitrogen were actually stored by the maternal organism in this case.

Immediately after birth the nitrogen balance, as indicated in the chart, changes to the negative side, corresponding to the period in the metabolism when the antiferment titer rapidly falls, a time too, when the uterus must be digested back to its normal size.

The sequence of events — lowering of the lipase activity, accumulation of lipoids in the serum, increase in the antiferment titer, checking of protein metabolism, the retention of nitrogen — seems simple and logical.

Coincident with these changes, certain definite alterations occur in the titer of the proteolytic serum ferments: (*a*) the ereptase or peptidase is increased to from two to four times the normal, throughout pregnancy, and remains at a constant level during delivery and the puerperal period, when uncomplicated; (*b*) the protease is increased to a small extent early in pregnancy and reaches a maximum immediately after delivery. In the following table the average values for a series of pregnant women gives an idea of this relation (protease).

SERUM DIGESTION (CHLOROFORM METHOD AT 47 C., 24 HOURS)

Before delivery	0.03 mg. per c.c.
1st day following	0.08 mg. per c.c.
10th day following	0.00 mg. per c.c.

This corresponds in general to the findings of the Abderhalden reaction, which is also augmented immediately after the delivery.

Do these serum changes influence a coexisting tuberculous process? It is an accepted clinical observation that pregnancy, and particularly parturition, are decidedly detrimental to the tuberculous woman, the most pronounced activity developing as a rule immediately after delivery or shortly after the puerperium. Even early in the pregnancy, cases which have been arrested are apt to give evidence, on careful examination, of focal activity while the general symptoms may remain suppressed.

The reaction involving the balance that has been discussed as obtaining in the tubercle may be described somewhat as follows: During the early stages of pregnancy the protease begins slowly to attack the fibrous connective tissue wall of the tubercle, small amounts of toxic material are liberated from the caseous focus, this in turn causing some local reaction on immediately adjacent tissues. This effect of the protease is counterbalanced to some extent by the coincident increase in the antiferment, and also by virtue of the increase in the ereptase as a result of which the body is able to take care of a certain amount of toxic split products. The net result of the altera-

tion of the ferment balance is a condition in which we may have a focal activation but also a more or less complete detoxication of the patient and feeling of well being. This may continue until the time of delivery. At this period two fundamental changes occur: (1) the antiferment is diminished, and (2) a marked mobilization of protease takes place, both changes that favor proteolysis in the body. The more resistant connective tissue is now rapidly digested, partly autolyzed toxic split products as well as bacteria are in consequence released and absorbed in some quantity, and the conditions are most

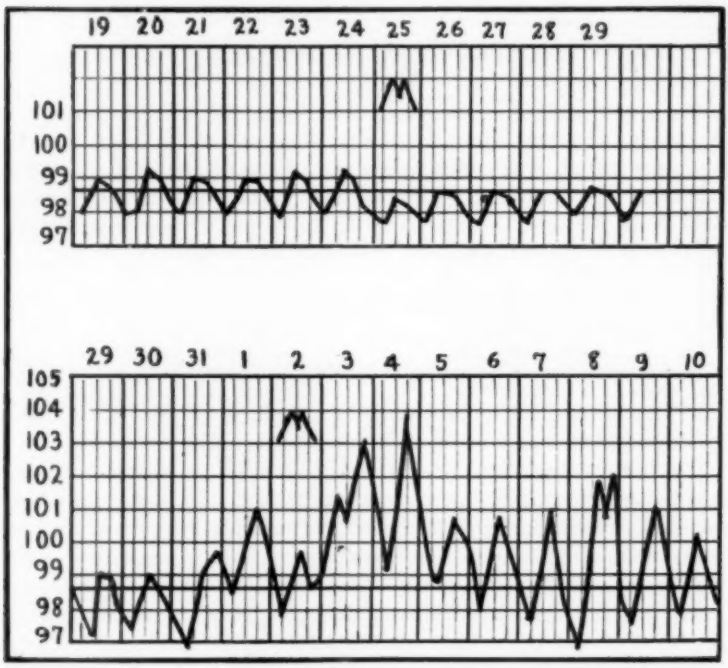


Chart 2.—Effect of menstruation on the temperature curve of the tuberculous woman (after Pottenger). M—— day of menstruation.

favorable for the rapid progress of the disease. During this time the ereptase has not increased, and an accumulation of the toxic products may take place because their destruction is delayed. In other words, the ferment-antiferment balance of the serum has been altered to such a degree that the local process is influenced unfavorably.

This explanation along lines of ferment observation coincides exactly with clinical observation and the underlying facts have been established in a number of laboratories.

We may now take another example, less complicated, because in it the antiferment changes do not take place to any extent and we have to deal solely with an increase in the proteolytic ferment. It is known that the Abderhalden reaction becomes positive in every female for a period varying from three days to one week before menstruation, then promptly becomes negative again.[5] The effect of the menstrual cycle on the temperature of the tuberculous woman is also a well known clinical phenomenon. In incipient cases we usually find a slight increase in temperature just preceding menstruation; in advanced cases a stormy febrile reaction lasting a week or more may be ushered in. The two charts (Chart 2) which are from Pottenger's book,[6] illustrate such cases. Here again, the proteolytic ferments are evidently able to attack connective tissue, expose the necrotic foci and with the coincident hyperemia wash into the circulations some of the toxic split products that have accumulated.

These two examples — pregnancy and the menstrual cycle — have been made use of here simply to make clear the one fact that we are dealing with conditions in which immunologic factors, as usually understood, are not concerned, so that these temperature reactions and activation of latent foci need bear no relation to antibody reactions, and we may dispense with them for the time being in the discussion of these special conditions.

THE TUBERCULIN REACTION

When Koch introduced tuberculin in the therapy of tuberculosis he did so with the clear-cut idea of inducing an active immunization. Under the method of administration as recommended by him, active immunization did occur. That is, a demonstrable increase in antibodies — bacteriolysins, agglutinins and precipitins — was noted, but despite this augmentation patients frequently went to a fatal termination under circumstances that warranted the belief that the tuberculin treatment had harmed them.

We have at present no clear-cut evidence that resistance to an established tuberculosis is related to antibody concentration of the serum or tissues. Titze[7] as a result of extensive animal experiments says "nothing speaks with any certainty for the fact that the organism destroys the invading tubercle bacilli through the agency of antibodies

5. Baumann, E.: Monatschr. f. Geburtsh. u. Gynäk., 1915, **42,** 199. Van Waasbergen, G. H.: Monatschr. f. Geburtsh. u. Gynäk., 1915, **42,** 230. Kjaergaard, S.: Zentralbl. f. Gynäk., 1914, **38,** 264. Engelhorn, E., and Wintz, H.: München. med. Wchnschr., 1914, **61,** 689.

6. Pottenger, F. M.: Pulmonary Tuberculosis, 1908, William Wood & Co., New York.

7. Titze: Berl. Tierärtztl. Wchnschr., 1912, No. 30.

or of phagocytosis . . . healing is rather to be sought in the fixation of the bacilli by the tissues." Haupt[8] Schürr,[9] Citron[10] and other investigators have come to the conclusion that resistance to tuberculosis does not parallel the antibody concentration.

If, then, tuberculin therapy is a valuable therapy, its effect probably depends on factors that are not related to the specific antibodies. Bessau[11] has recently reviewed the subject in a helpful manner. He calls attention to the fact that the tuberculin reaction is not related to our ordinary conception of specificity or immunity, because, in the first place, we cannot sensitize animals to tuberculin; secondly, that tuberculin contains no native protein — only polypeptids — and finally, that it has been practically impossible to transfer passively the sensitization of tuberculous animals to normal animals (Klopstock,[12] Landmann[13]). Hamburger had recognized the resistance that follows the repeated injections of tuberculin as an antianaphylactic phenomenon; nonspecific, independent of dosage, but depending rather on the reaction induced. Bessau rightly emphasizes the differences between the general and local reactions to tuberculin; in progressive tuberculosis, for instance, the general reaction may become more pronounced while the local reactions may be extinguished, and vice versa. While supposedly a method of active immunization, Bessau declares that the only effect is to produce a tuberculin resistance, which in a nonspecific way may be of benefit.

Aronson[14] concludes as a result of the extensive investigations that he has carried out that the tuberculin reaction does not depend on antibodies; that the general reaction is not specific but is related to the disintegration of leukocytes about tuberculous foci; he concedes that there is an element of specificity in the cutaneous reactions. This latter deduction he draws from his experiments with tuberculin digested with pepsin-hydrochloric acid. This preparation was still able to induce a general but not a local reaction.

To summarize the conclusions of the more recent workers the following would seem to be the concensus of opinion: (*a*) the clinical course need not be influenced by the antibody concentration; (*b*) the tuberculin reaction does not depend on the antibody titer of the serum; (*c*) the general and local reactions are not comparable; (*d*) and tuberculin does not immunize, but the resistance to tuberculin established

8. Haupt, H.: Ztschr. f. Tuberk., **22,** 209, 363, 463.
9. Schürr, J.: Deutsch. Arch. f. klin. Med., 1912, **109,** 112.
10. Citron, J.: Deutsch. Arch. f. klin. Med., 1913, **110,** 184.
11. Bessau, G.: München. med. Wchnschr., 1915, **62,** 323.
12. Klopstock, F.: Ztschr. f. exper. Path. u. Pharmakol., 1914, **15,** 13.
13. Landmann: Deutsch. med. Wchnschr., 1912, **38,** 1245.
14. Aronson, H.: Deutsch. med. Wchnsch., 1914, **40,** 487.

during tuberculin treatment may possibly influence the existing tuberculosis in a nonspecific manner.

Two further experiments firmly establish these deductions. Bail showed that if a tubercle is implanted in a normal animal it at once reacts to tuberculin with a general reaction, that is, before either sensitization or immunization could possibly occur. More recently Klemperer[15] has definitely excluded both the cellular and humoral antibody complex in the tuberculin reaction when he demonstrated that, when in animals the single tubercle is extirpated, the tuberculin reaction is extinguished at the same time. This experiment is undoubtedly of primary importance.

Before entering into a theoretical discussion of the possible mechanism involved it may be well to briefly review certain facts in regard to tuberculin. The first of these concern the question as to the specificity of the reaction.

SPECIFICITY

Feistmantel extracted an acid-fast streptothrix and obtained an active tuberculin. On the other hand, leprous and actinomycotic patients are said to react strongly to tuberculin. The tuberculous individual will react to many of the following substances injected either subcutaneously or intravenously with a typical tuberculin reaction and constitutional symptoms, while the nontuberculous individual will tolerate equal doses without reaction; these include the following: Hypertonic salt solution; distilled water; iodids; some colloidal metals; protein split products; ferments; immune (tuberculous) serum; heterologous serums; exudates; photodynamic insults (heliotherapy, roentgen rays, deep red rays, etc.).

Nor must it be supposed that this nonspecificity is limited solely to the general tuberculin reaction. Tenzer,[16] for example, noted that in 73 children, of whom 48 reacted positively to the von Pirquet, 22 gave a comparable reaction with Witte peptone. In another series of 69, of whom 34 reacted positively to the von Pirquet, 19 gave a reaction with cholera vaccine used in place of the tuberculin. These nonspecific reactions occurred only in the von Pirquet positive children. There is here distinct evidence that an increased susceptibility of the skin obtains which is wholly independent of specific factors. Petersen[17] also calls attention to this fact, and Burnet[18] has studied the relation of the skin and general reactions in the lower monkeys, noting that while the general reaction might be positive in these animals during all stages of

15. Klemperer, F.: Beitr. z. klin. d. Tuberk., 1914, **30,** 431.
16. Tenzer, E.: Monatschr. f. Kinderh., 1911, **10,** 131.
17. Petersen, H.: Hospitalstid., 1912, **5,** 421.
18. Burnet, E.: Compt. rend Soc. de biol., 1912, **72,** No. 28.

the disease, the skin reactions were negative throughout all stages of sensitization and disease. Observations such as these led Torrenson[19] to use Witte peptone instead of tuberculin in the treatment of tuberculosis of the skin; his results, carried out on a limited number of patients, were satisfactory.

Experiments carried out by Matthes[20] more than twenty years ago were along similar lines. Matthes injected small amounts of albumoses into tuberculous guinea-pigs and found that a violent focal reaction occurred about each tubercle, followed by profound intoxication, loss of temperature and death in a short time. In the normal animal only a slight and transient rise in temperature was observed. These studies, really of the utmost importance in the study of the mechanism of the reaction, have been generally ignored.

Probably of equal importance is the fact that the von Pirquet reaction is never augmented by immune tuberculosis serum when it is added to the tuberculin immediately before, or when incubated with the tuberculin before innoculation (the serum may be derived from immune animals or from patients in the various stages of the disease, with or without tuberculin treatment), but is invariably delayed when such serums are added. (Petrova,[21] Aronson,[14] etc.) The only activating substances are lipoidal in nature as described by Bing and Ellermann.[22]

We are probably justified in concluding that the general reaction to tuberculin rests on factors largely nonspecific and that a nonspecific element enters also into the cutaneous tests. When we turn to survey the factors that render the tuberculin reaction negative we find that this resistance is wholly nonspecific.

INHIBITION OF THE TUBERCULIN REACTION

Von Pirquet observed that during measles and streptococcus infections the tuberculin reactions became negative; Brandenberg[23] found this to be true for scarlet fever, and Krannhals[24] as well as Glintschikow[25] observed the same condition in typhoid, pneumonia and acute articular rheumatism. Cozzolino,[26] working with pertussis and Moltschanoff[27] with diphtheria and serum sickness, also observed this phenomenon. The resistance to tuberculin during and following serum

19. Torrenson, E. G.: Abst., Ztschr. f. Immunitätsforsch., 1912, **5,** 1020.
20. Matthes, M.: Deutsch. Arch. f. klin. Med., 1894-1895, **54,** 39.
21. Petrova, M. K.: Abst., Ztschr. f. Immunitätsforsch., 1914, **6,** 1014.
22. Bing, H. J., and Ellermann, V.: Biochem. Ztschr., 1912, **42,** 289.
23. Brandenberg, F.: Deutsch. med. Wchnschr., 1910, **36,** 561.
24. Krannhals: München. med. Wchnschr., 1910, **57,** 836.
25. Glintschikow, W. J.: Abst., Ztschr. f. Immunitätsforsch., 1916, **8,** 509.
26. Cozzolino, O.: Abst., Ztschr. f. Immunitätsforsch., 1914-1915, **8,** 310.
27. Moltschanoff, W. T.: Jahrb. f. Kinderh., 1912, **75,** 434.

reactions in children was confirmed by Luithlein.[28] We are evidently dealing here with a general state of resistance to the local and in part the general tuberculin reactions during practically all the acute infections, during certain of the cachectic conditions, and following protein shock reactions (serum reactions).

In order to examine this relation to the problem before us we may revert to the second figure or curve in Chart 1 and study the material collected by Stern.[29] Stern determined that 65 per cent. of the women at his clinic (nonpregnant) gave a positive tuberculin reaction, that this percentage in the pregnant women decreased progressively to term and that immediately following delivery the percentage reacting positively began to increase until in women in the fifth and sixth day of the puerperium 67 per cent. gave the reaction. We have here definite evidence that a progressive resistance occurs during pregnancy and that this resistance vanishes in a surprisingly short period of time after delivery. It will be observed in the chart how closely this relation parallels the rise in the antiferment titer. Stern was familiar with the increase in the blood lipoid content during pregnancy[1] and suggested that the resistance was due to a binding of the antibodies to these lipoid bodies. It is apparent from these observations that the resistance to the tuberculin reaction (both general and local) need not depend on specific factors as might be surmised were we to observe it exclusively following repeated tuberculin injections.

EFFECT OF TUBERCULIN ON THE NONTUBERCULOUS ANIMAL

We are more or less familiar with the effect of tuberculin on the tuberculous organism and are apt to overlook the fact that tuberculin may develop marked reactions in the metabolism of the normal animal. That this is the case has been demonstrated by Mircoli.[30] Mircoli used tuberculin and also tubercle bacilli (killed) and injected these in small doses into normal experimental animals. The injections were followed by a short negative phase (especially when the dose was large) during which time the animals lost weight as compared to the controls; this was followed by a longer period during which the weight of the treated animals increased over that of the control animals. When repeated small doses were given, resistance developed, and the negative phase diminished, the animals showing a decided gain in weight as compared with the untreated animals.

28. Luithlein, F.: Wien. klin. Wchnschr., 1914, **27,** 493.
29. Stern, R.: Ztschr. f. Geburtsh. u. Gynäk., 1910, **66,** 532.
30. Mircoli, St.: Pathologica, 1914, **5,** 118.

THE DIRECT EFFECT OF TUBERCULIN ON AUTOLYSIS

Finally, it has been observed that tuberculin can influence autolytic processes directly. Pesci[31] added tuberculin (and other toxins) to autolyzing organ emulsions and found that the rate and magnitude of the process was increased in a degree proportional to the amount of tuberculin added. This effect seems to have some relation to the lipoids of the substrate. It is known that the lipoid solvents, including alcohol, will, when added to autolyzing organs, reduce the latent period of autolysis, presumably by destroying a lipoid-protein combination that normally resists autolysis (Chiari[32]), and which, under ordinary conditions, is only destroyed when a sufficient degree of acidity has developed. Pesci observed that in his tuberculinized substrate the neutral fats and fatty acids tended to decrease within fifteen minutes while the soaps increased, as compared to the normal autolysis. Barlocco[33] observed a similar lipoid rearrangement during autolysis when diphtheria toxin had been added to the substrate.

THEORETICAL CONSIDERATIONS

The facts which have accumulated as a result of both experimental and clinical investigation make it apparent that we must seek an explanation along lines not necessarily associated with the usual conception of immunity. In the first part of this paper evidence has been presented which indicates that the proteolytic ferment and the antiferment exercise a considerable influence on the tuberculous process. Is it possible that changes in the ferment-antiferment balance may be responsible for some of the phenomena observed in the tuberculin reaction?

We must keep in mind that tuberculin is not a native protein, but consists largely of polypeptids and must essentially be a toxic substance; as Turban says: "A preparation which is nontoxic and yet potent, is unknown." There is evidence that the activity of the various tuberculins is in proportion to their surface tension, which, in so far as tissue effect is concerned, simply means that the more diffusible products are the more toxic.[34]

In its essentials the tuberculin injection might be supposed to lead to the changes which we associate with the typical protein "shock" reaction, that is, it would result in (*a*) a mobilization of the proteolytic ferments, (*b*) in a primary reduction followed by a subsequent increase in the antiferment titer, and (*c*) in the development of a non-

31. Pesci, G.: Pathologica, 1911, **3**, 144, and Zentralbl. f. Bakt., Part 1, Orig., 1911, **59**, 186.
32. Chiari, Rich.: Arch. f. exper. Path. u. Pharmakol., 1908-1909, **60**, 257.
33. Barlocco, A.: Pathologica, 1911, **3**, 7.
34. Kollert, Victor: Beitr. z. Klin. d. Tuberk., 1914, **30**, 173.

specific resistance comparable to the "antianaphylaxis" or the "desensitization" of the immunologist. Graphically, these changes can be illustrated as in Chart 3; that is, following the injection we might expect a period when proteolytic activity is favored — lowering of the antiferment and increase in the protease — followed by a zone of several days' duration during which time the reverse holds true. During this latter time the ereptase might be augmented, which theoretically would aid in detoxication by eliminating the higher split products.

We know that the use of small doses of tuberculin at definite or varied time intervals has been established in routine as the result of a vast accumulation of clinical experience, largely empirical, and we are

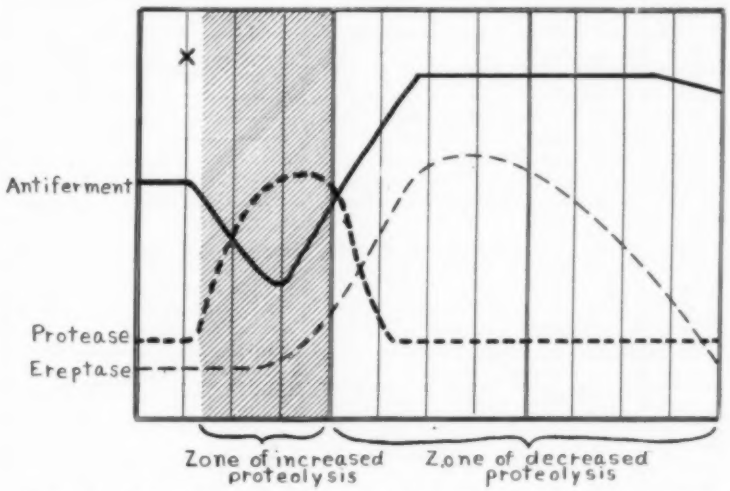


Chart 3.—Schematic relation of serum ferment and antiferment following tuberculin injection.

justified in believing that it represents the most favorable method of its use. With this method we can undoubtedly produce a tuberculin resistance or tolerance in the tuberculous individual; that is, as the result of repeated stimulation of this kind the organism becomes more and more resistant to intoxication. It has been the general impression that, because anaphylactic phenomena are so strikingly specific, the resistance following shock is equally specific. This, however, is not true. The most recent work, especially that of Bessau and his associates,[35] has shown that antianaphylaxis is practically nonspecific. The state of desensitization, or the refractory period following anaphy-

35. Bessau, G., Opitz and Preusse, O.: Zentralbl. f. Bakt., Part 1, Orig., 1914, **74**, 162, 310.

lactic shock, occurs also following the injection of anaphylatoxins and similar protein poisons; Vaughn noted the same general phenomenon when injecting his protein split products; repeated sublethal doses increasing the resistance until one or possibly two times the fatal dose could be tolerated.

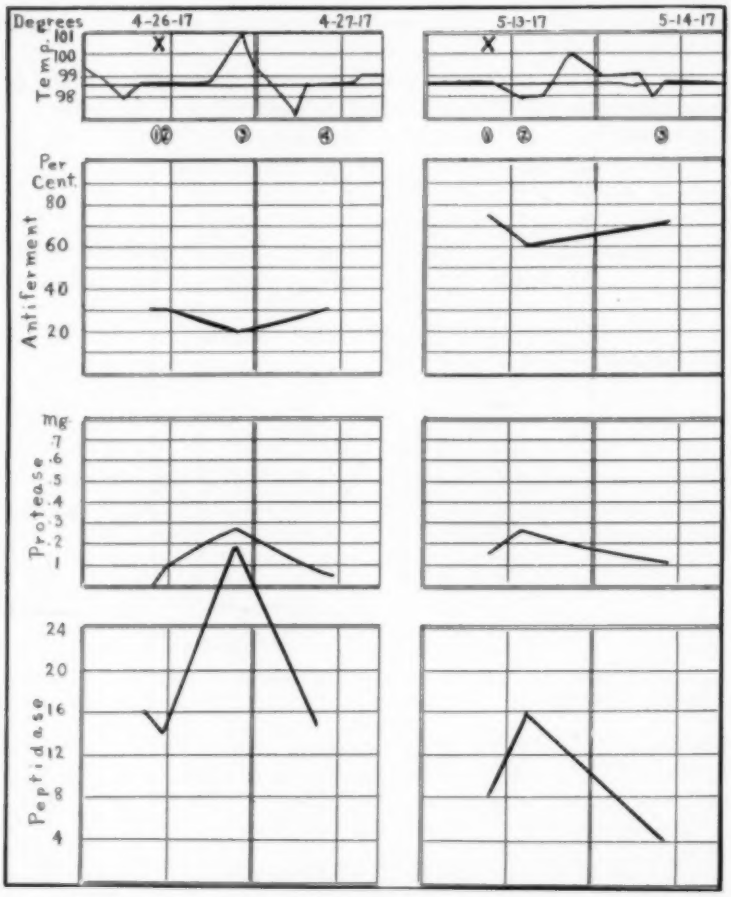


Chart 4.—Effect of tuberculin injection on serum ferment and antiferment.

It had been observed, first by Rusznjak[36] that the serum antiferment titer was markedly augmented after anaphylactic shock, to which fact Rusznjak in part attributed the increased resistance to the refractory

36. Rusznjak, S.: Deutsch. med. Wchnschr., 1912, **38**, 168.

period. Jobling[37] made similar observations following a variety of protein shock poisons and showed, furthermore, that when the antigen was mixed in vitro with an antiferment before injection into the animal, anaphylactic shock could in many instances be averted. It seems reasonable at any rate to assume that where we are dealing with an intoxi-

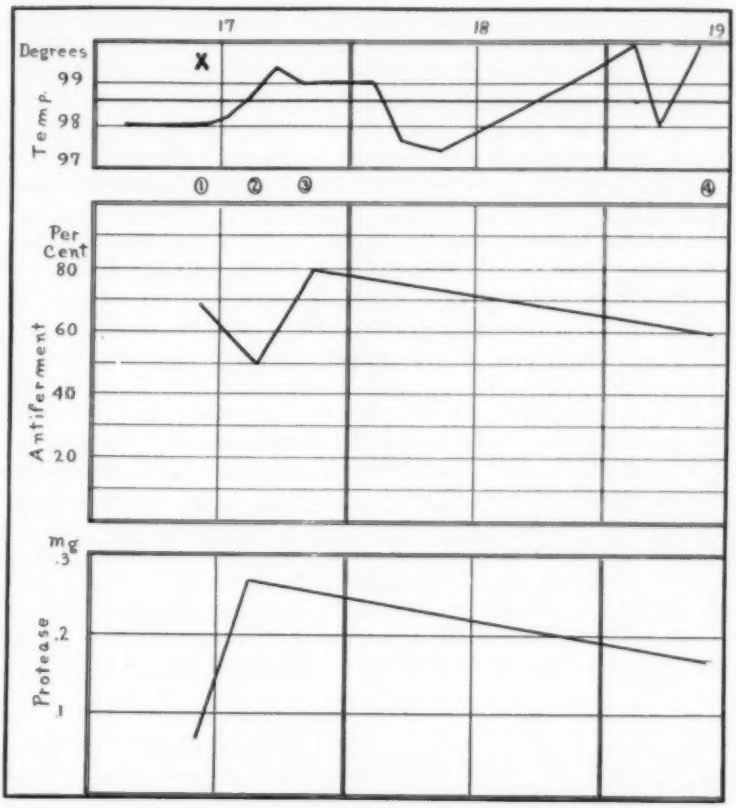


Chart 5.—Serum alteration following tuberculin injection.

cation having its origin in protein splitting in the body, an increase in the antiferment, that is, in those substances which inhibit or delay proteolytic activity, would be one of the factors involved in this resistance.

We could assume that the tuberculin reaction takes place somewhat as follows: When tuberculin is injected subcutaneously a certain number of cells are injured and some protease is liberated. This, just as it

37. Jobling and Petersen: Jour. Exper. Med., 1914, **20**, 468.

takes place physiologically during the menstrual period, is carried to the tuberculous focus, and, by digestion there, produces the typical focal reaction and with it a liberation of toxic material and general malaise. We must keep in mind, too, the possibility of the direct activating influence of the tuberculin on autolytic processes. At any rate we deal not with a condition of sensitization of the tissues of the body as a whole, but solely with the slight breaking down of tuberculous tissue at some point, the degree depending on the relative amount of ferment mobilized, on the relative vascularization, and on the amount of connective tissue that protects the focus. Thus, the reaction would be negative in the nontuberculous, for here, when a ferment mobilization does occur it finds no pathologic focus to attack, no protein is broken down and no febrile reaction occurs. In the tuberculous patient we have, furthermore, a cumulative effect when the ferment-antiferment balance is altered, because the liberated toxic material will add a secondary protein shock which is lacking in the normal person.

While it is apparent from these considerations that we may be dealing with a reaction that is nonspecific, in that the means used to elicit it are not specific, it is immediately apparent that the reaction itself resulting from the stimulation of the tuberculous focus implies a specific stimulation in the true sense of the term, in that disintegrating bacilli, and possibly even living bacteria, are absorbed from the focus, whether that focus is stimulated as a result of heliotherapy, of immune serum, of iodin or of tuberculin. As far as immunologic investigation has gone it seems certain that immunization brought about as the result of the incorporation of whole organisms, either living or dead, has given the most satisfactory results in protection experiments. It is essential at any rate to keep in mind this dual effect of the tuberculin reaction, the specific phenomena following in the wake and as a result of the effect of the nonspecific reaction.

REPORT OF EXPERIMENTAL CASES

Case 1.—F. L., male, white, aged 18 years, had tuberculosis of the kidney (kidney removed six months previously). Cystoscopic examination revealed tuberculosis of the bladder. There was no active pulmonary involvement. One mg. old tuberculin was given subcutaneously at 10 a. m. Serum taken at 10 and 11 a. m., 10 p. m. and 10 a. m. the following day. The examination of the serum revealed the changes in the ferment titer charted in Chart 4, A.

It will be noted that the antiferment titer was diminished by evening, when the maximum temperature was recorded. The protease increased from 0 to 0.27 mg. per c.c. during this time, while the peptidase, which was originally fairly strong, increased to about twice the original titer. This increase was not maintained the following day. Two weeks later a second injection (2 mg. O. T.) was made and similar serum alterations followed this injection (Chart 4, B).

Case 2.—H. V., man, white, aged 52, had unilateral pleurisy with a large amount of hemorrhagic exudate, which was withdrawn by puncture. The clinical course was afebrile, with occasional periods of temperature to 100 F. for one or two days. He was given 1 mg. O. T. subcutaneously. No increase

of temperature was observed, but considerable malaise and headache followed. The serum alterations have been recorded in Chart 5. There was a distinct decrease in the antiferment for several hours after the injection, then a slight increase in the evening. The protease increased following the injection. No clinical effect was observed from the small dose used.

For comparative purposes the following two cases are of interest:

CASE 3.—J. R., a white man, aged 45 years. Physical findings revealed bilateral pulmonary involvement with cavity formation, but absence of tubercle bacilli in the sputum. There was a considerable range of temperature, marked cough and expectoration. He was given 1 mg. O. T. subcutaneously. This

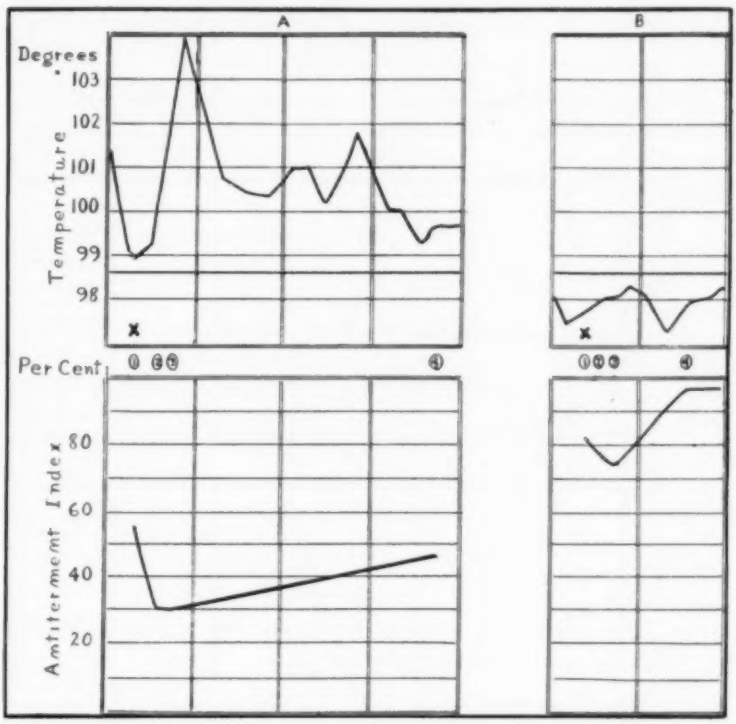


Chart 6.—Antiferment alteration in case unfavorably (*a*) and favorably (*b*) influenced by tuberculin.

was followed by a rise in the temperature as well as physical findings of focal activation, which continued for several days. Clinically this patient was not improved after the injection; indeed, the general feeling of malaise and discomfort seemed increased.

When the antiferment curve is examined (Chart 6, A) it will be observed that the decrease persisted for a considerable time and even after three days had not returned to the original titer. When contrasted with the following case this fact is of interest.

Case 4.—F. B., a white man, aged 40, with arrested bilateral apical lesions and general visceroptosis, entered the hospital because of gastric distress. The temperature curve was persistently subnormal. He was given 2 mg. O. T. subcutaneously, followed by no temperature or constitutional effect. It will be noted that the antiferment (Chart 6, B) after the initial decrease, reached a level that was considerably higher than before the injection.

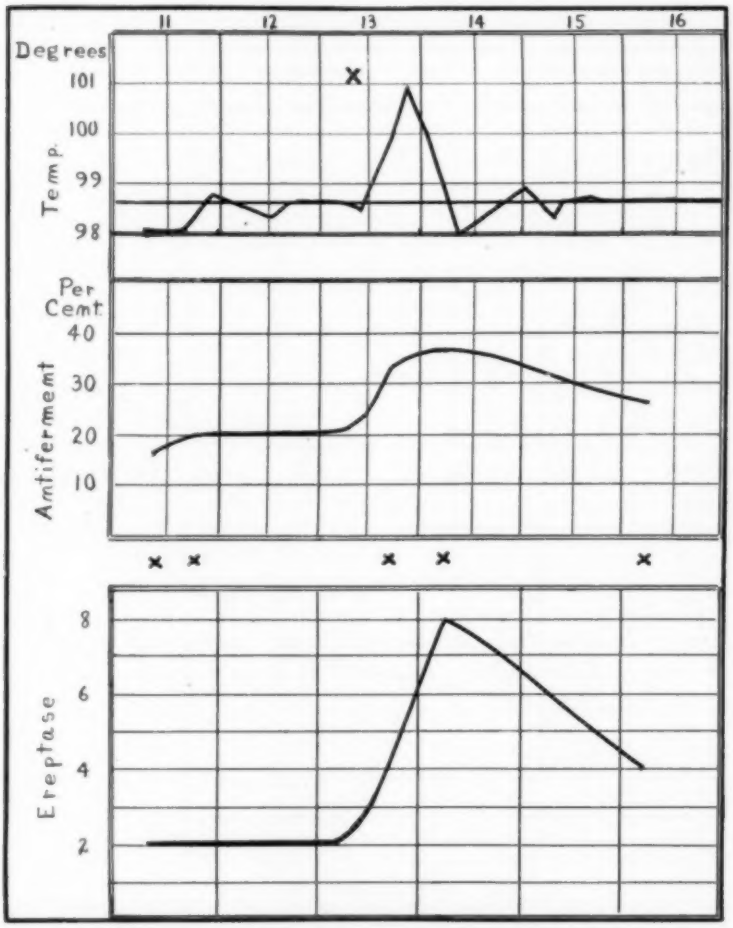


Chart 7.—Serum alteration following tuberculin injection.

The serum changes that occur following the injection in a fairly active case with well defined clinical improvement following the injection are illustrated in Chart 7.

CASE 5.—O. V., a white man, aged 24, had tuberculosis of the peritoneum. He entered the hospital with a considerable febrile temperature range, emaciated, and with a large exudate in the peritoneal cavity, which was removed at two separate times. With rest the patient improved progressively until the temperature remained practically normal. At this time he was given 1 mg. O. T. subcutaneously which was followed by a sharp temperature reaction (101 F.). Blood samples had been collected at several periods previous to the injection; they were also taken in the evening of the day of injection, the following morning and on the third day following.

It will be observed that the antiferment increased considerably and that the rise persisted for at least three days after the injection. The protease was not determined but the ereptase increased after the injection and continued at a high level for the day following. The patient said he felt improved, and objectively seemed so.

In several syphilitic cases the serum alterations following the tuberculin injection (2 to 5 mg. O. T.) have been similar in character.

In fifteen cases in which the serum reaction has been studied following tuberculin injection, of which the charted cases are representative, either one or more of the ferment-antiferment changes suggested as possibilities in the theoretical discussion, have been observed. The decrease in the antiferment has been found to be the most constant alteration; in the cases unfavorably influenced by the tuberculin no increase followed the original decrease; in the cases clinically improved a well-marked rise usually follows. The changes in the ferments — protease and ereptase — are less constant, but usually at least one of these ferments makes its appearance, the ereptase in particular being increased in the cases which give evidence of benefit from the reaction.

It might seem warranted to consider the tuberculin reaction as a two-phase phenomenon in the tuberculous individual. The primary alteration of the ferment-antiferment balance brings about a medium favorable for proteolysis in and about the tubercle. Digestion and the liberation of toxic material result and are reflected in the constitutional effects. In the nontuberculous individual it is probable that the primary serum alterations also occur, but the digestive ferments, finding no focus to attack, liberate no toxic material and no general reaction is elicited.

CORRELATION

From the evidence presented it seems probable that the ferment mobilization, however produced, will influence the tuberculous focus and bring about a general reaction if the digestion be of sufficient degree. From this point of view we can understand the undeniable lack of specificity associated with the general reaction; any agent that will bring about a ferment-antiferment balance favorable for proteolysis will effect a general reaction provided the focus be sufficiently unstable. That the various vaccines, protein split products and even

inert physical agents will do this has been demonstrated.[38] Similarly, Pfeiffer[39] observed such changes following burns of varying intensity, making it apparent why, when a patient during the course of heliotherapy burns to a moderate degree, a tuberculin reaction with focal and general effects may result. Conversely we can understand that in any infectious granulomas in which a balance exists similar to that obtaining in the tubercle, the injection of tuberculin will be followed by a marked febrile reaction.

If we assume that proteolytic factors enter also into the local cutaneous reactions, then an increase in the antiferment would operate to oppose such a reaction and render it negative. This seems evident when we keep in mind the increase in the antiferment that takes place during the course of a physiologic process (pregnancy), during disease (acute infections) and following induced protein "shock" or tuberculin reactions, and the inhibition of the tuberculin reactions during these conditions. In the late stages of tuberculosis this same increase in antiferment is observed (coincident with the decrease in the lipases Marutaew,[40] Bauer[41]), and the local reactions to tuberculin become less evident while the general reaction may become more severe, because of the lability of the numerous foci. The participation of the proteolytic ferments in the local reactions is also made probable in that any antiferment added to the tuberculin before its local application (sodium oleate and serum) will invariably delay the reaction. The recent work of Sherrick,[42] of Stokes[43] and of Burroughs and Neymann[44] will, however, probably materially modify our present conception of skin reactions, so that any discussion at present is out of question in this particular domain. Sherrick observed that he could obtain a positive luetin reaction in all iodized patients, and that the injection of agar and starch gave a reaction as well. He noted that a patient who under normal conditions reacted to the luetin with a diffuse areola went on to complete pustule formation under iodids. This work has been repeatedly confirmed.[45] For reasons given early in this paper we assume that the iodin and iodid act therapeutically by lowering the antiferment of the blood and tissues when given in gradually increas-

38. Jobling, Petersen and Eggstein: Jour. Exper. Med., 1915, **22,** 597.
39. Pfeiffer, H.: Ztschr. f. Immunitätsforsch., Orig., 1915, **23,** 473.
40. Marutaew, A. S.: Abst., Ztschr. f. Immunitätsforsch., 1913, **7,** 90.
41. Bauer, J.: Wien. med. Wchnschr., 1913, **36,** 2197.
42. Sherrick, J. W.: The Effect of Potassium Iodid on the Luetin Reaction, Jour. Am. Med. Assn., 1915, **65,** 404.
43. Stokes, J. H.: Jour. Infect. Dis., 1916, **18,** 402.
44. Burroughs, M. T., and Neymann, C. A.: Jour. Exper. Med., 1917, **25,** 93.
45. Kolmer, J. A., Matsunami, T., and Broadwell, S.: The Effect of Potassium Iodid on the Luetin Reaction, Jour. Am. Med. Assn., 1916, **67,** 718. Kolmer, J. A., Matsunami, T., and Immermann, S., and Montgomery, C. M.: Jour. Lab. and Clin. Med., 1917, **11,** 401.

ing doses,[46] and from this point of view the observations made by Sherrick and others are readily understood, in that a lowering of the threshhold of proteolysis would bring about a condition when instead of the luetin producing a simple inflammatory reaction, the process would go on to complete pustule formation and necrosis when the antiferment "brake" was released. The observation of Burroughs and Neymann is of equal importance in that they have demonstrated that amino-acids in sufficient concentration may be toxic for cells. Inasmuch as the rate of diffusion in the cutaneous tissues is slow, it is readily understood that a sufficient concentration of such lower split products might accumulate and result in toxic manifestations quite different from those observed when dealing with the organism as a whole.

The alterations following tuberculin therapy probably bring with them two general effects: (*a*) the rate of nitrogen metabolism is decreased and a storage of nitrogen may result, as indicated in the work of Mircoli; (*b*) the reaction, even if local and without apparent constitutional effect, increases the antiferment gradually and in this way not only increases the resistance to following injections, but increases the resistance at the focus against digestion and intoxication.

With this idea in mind one can understand why many clinicians have, as a result of clinical experience alone, come to realize that in tuberculin therapy they are not dealing with a specific effect and are not primarily immunizing the patient against the tuberculous infection. The nonspecificity of the reaction that follows tuberculin injections has recently been taken advantage of by Browning[47] in dealing with patients highly susceptible to tuberculin, who nevertheless insisted on tuberculin treatment. In such cases Browning has found that by interpolating several doses of typhoid and other vaccine, he was able to increase the following tuberculin doses very materially without undue reaction on the part of the patient.

It is interesting to recall in this connection that tuberculin can be used interchangeably, to a certain degree, with other agents that bring about an alteration in the ferment-antiferment balance and thereby induce therapeutic effects. One needs but mention the use of tuberculin in syphilis (Biach[48]) and the effect said to be noted in paresis (von Wagner[49]). The results of von Wagner have been confirmed from many sources (Döllken,[50] Battistessa[51] and Jukow[52]). We have, fur-

46. Jobling and Petersen: The Therapeutic Action of Iodin, THE ARCHIVES INT. MED., 1915, **15**, 286.
47. Browning, C. C.: Los Angeles (Personal communication).
48. Biach, M.: Wien. klin. Wchnschr., 1915, **28**, 1345.
49. Von Wagner: Wien. med. Wchnschr., 1909, **59**, 2125.
50. Döllken: Berl. klin. Wchnschr., 1913, **50**, 962.
51. Battistessa, P.: Riv. ital. di Neuropatol. psichiat. ed elettroter., 1912, **5**, 117.
52. Jukow, N. A.: Abst., Ztschr. f. Immunitätsforsch., 1913, **7**, 558.

thermore, to keep in mind the well-known phenomenon of the activation of tuberculous lesions in diseases associated with an increased amount of proteolytic ferments in the serum, as, for instance, in dementia praecox and in carcinoma, Lubarsch having called attention to this latter fact.

ANIMAL EXPERIMENTATION

Inasmuch as practically all of the experimental work in tuberculosis has been done on the smaller experimental animals (guinea-pigs and rabbits) it may be well to discuss briefly the relation of the serum ferments in these animals and the effect on the tuberculosis problem.

Guinea-pig serum (and also rabbit serum, to a lesser degree) differs widely from the human in containing much less antiferment, more lipase and vastly more proteolytic ferment — both protease and ereptase. Under such conditions we should expect that the connective tissue fixation and encapsulation would be made more difficult because of the pronounced digestive effect of the serum. On the other hand, abscess formation might be expected to lead to caseation even with nontuberculous processes (the leukocytes of the guinea-pig contain no leukoprotease) if the permeability of the focus is not sufficient to permit the free entrance of serum. These are of course the actual conditions to be observed in pathologic conditions in these animals and constitute one of the chief reasons why the results of animal experimentation cannot be applied with any degree of certainty to the tuberculosis of man.

It is only when serum alterations are produced in the guinea-pig so that it resembles the condition in man that the picture of the tuberculous process offers a similarity to that of the human form. Helen Baldwin and Elise L'Esperance[53] have recently published observations that are of interest in this connection. By producing an occasional protein shock (with typhoid vaccine) they found that the treated animals gained in weight over the control animals, and that the tuberculous lesions showed a marked fibrosis, an appearance quite unusual in the tuberculosis of these animals. The results are probably to be accounted for by the decided increase in the antiferment following such typhoid injections, which would tend to preserve the connective tissue encapsulation and thus aid in the fixation of the bacteria.

Experiments such as these serve to bring out the fact that a sharp difference exists between an immunity against the establishment of an infection and the resistance to an infection already established. The guinea-pig, practically immune to spontaneous tuberculosis, possibly just because of the abundance of the serum ferments, by this very fact is enabled to offer little resistance once the infection is established,

53. Baldwin, Helen, and L'Esperance, Elise: Jour. Immunol., 1917, **2**, 283.

because the unfavorable serum balance prevents the fixation of the bacteria by connective tissue. Under such conditions immunization per se will have no practical effect on the development of an established infection, whereas a protein "shock" reaction as carried out by Baldwin and L'Esperance does seem to influence the pathologic picture to a considerable degree, offering one of those instances in which therapeusis along nonspecific lines may possibly offer more benefit than therapy carried out with strictly specific end objects.

THE RELATION TO THERAPEUSIS

The probable basis for the therapeutic effect of tuberculin has been discussed along the lines of the ferment alterations. Clinical use has varied from overindulgence to underindulgence, with the final establishment of the small dose in ordinary routine. There is, however, some evidence that occasional larger doses, with constitutional effects, may in certain instances be of greater benefit than the continual use of the very minute doses commonly in use. Such authorities as Bandelier and Roepke,[54] for instance, call attention to the feeling of well being and the objective clinical improvement that may follow such a general reaction in some individuals. The difficulty in predetermining just which cases may so react probably makes the current method of administration more suitable for routine use.

It may be of interest to note in how far more or less established empirical therapeusis has followed along lines that influence the ferment-antiferment balance. This can be divided into two general groups, the first having to do with fats and lipoids of various kinds. Czerny[55] in a very interesting paper has presented evidence that the immunity of the nursing infant to many of the ordinary infections is not due to immune bodies furnished in the milk of the mother, but is closely related and dependent on the fat constituents of the milk, which in some manner augment the resisting power of the infant. Among empirical remedies used in tuberculosis, fats have played a large rôle, including the highly unsaturated fish oils, milk, cream and the yolk of eggs; the use of phosphorus must be included in this category.[56] In the consideration of the value of just these substances it is interesting to recall that Fermi[57] noted the antiferment property of milk and eggs many years ago, and it can be demonstrated experimentally that the antiferment of the lymph is gradually increased after a meal of milk.

54. Bandelier and Roepke: Lehrbuch der spec. Diag. u. Therap. d. Tuberk., Ed. 8, Würzburg, 1915.
55. Czerny: Med. klin., 1913, 895.
56. Frank, L., and Schloss, E.: Jahrb. f. Kinderh., 1914, **79,** 539.
57. Fermi, C.: Centralbl. f. Bakteriol., Part 1, Orig., 1909, **50,** 225.

Braunstein and Kepinow[58] found that phosphorus increased the antiferment, and the increase in the antiferment following the continued use of the unsaturated oils seems logical considering the probable constitution of the antiferment lipoids. The feeding experiments of Weigert[59] are also of interest in this connection.

It is not within the range of this paper to discuss the relation of the lipases to the tuberculous infection, although the subject is intimately bound up with this particular phase of therapy and as such has been discussed by the Russian workers,[60] who seem to have devoted considerable study to the therapeusis of tuberculosis by means of the fat substances. Briefly, this therapy might be described as a method to increase the antiferment, to check proteolysis at the focus, and aid in the conservation of the connective tissue of the scar.

The second school, the foremost advocates of which we find among the French clinicians, has placed greater reliance on iodin and its compounds, but chiefly on free iodin.[61] Apparently such therapy has decided value in glandular tuberculosis, and with apparent reason. By this method of therapy the antiferment is probably reduced[46] and the connective tissue reaction about the focus lessened so that a slow and gradual exposure of the focus follows. If this focus be in lymphatic tissue where lipolytic activity is provided by the lymphocytes, the tubercle bacilli are probably destroyed when they are exposed to such activity; if the focus is in pulmonary or other nonlymphatic tissue the effect of the iodin may simply be in the nature of an autotuberculinization, in which digestion is first aided, then checked by the antiferment reaction that follows the digestion. Theoretically, this seems ideal therapy in the early case in which the body is able to withstand a certain amount of intoxicating material gradually absorbed.

If in this paper certain of the ferment and antiferment changes have been dwelt on, it has not been done with the idea that they represent the exclusive factors that effect the tubercle in its relation to the host. The digestive factors are at best but one of the many complex balances that have a rôle in the adjustment of the infected organism to the parasite, but having such a rôle, it may be well to keep the effect of these ferments and the antiferment in mind when we wish to study the effect of therapeutic measures on the pathologic process.

58. Braunstein and Kepinow: Biochem. Ztschr., 1910, **27,** 170.
59. Weigert: Berl. klin. Wchnschr., 1907, **44,** 1209.
60. Metalnikow, S. J.: Ztschr. f. Immunitätsforsch., Orig., 1914, **22,** 235.
61. Barbier: Ztschr. f. Tuberk., 1914, **22,** 433.

LIPODYSTROPHIA PROGRESSIVA*

IRVING J. SPEAR, M.D.
Professor of Neurology and Clinical Psychiatry, University of Maryland
BALTIMORE

The term "lipodystrophia progressiva" was first applied by Arthur Simons to a syndrome as described by him,[1] in 1911.

This condition is rather uncommon. Up to the present about twenty-four cases have been reported and the only case in American literature I have been able to find has been published by Herrman.[2] The most recent and comprehensive review of this subject is by F. Parks Webber,[3] who has collected all the reported cases and clearly discusses this condition, its probable causes, its course, the outlook in the various cases, and has reviewed them up to the time of his article and also several cases with which he was familiar but which had not yet appeared in the literature.

Lipodystrophia progressiva is a term applied by Simons to a syndrome beginning most frequently between the fifth and twelfth year, and chiefly affecting females. In this condition, there occurs a gradual, progressive emaciation, beginning in the face and progressing downward, involving the neck, shoulders, trunk and upper extremities, with, in most reported cases, an increased deposit of fat in the buttocks, thighs and — sometimes — the legs. The gradual disappearance of fat progresses until the appearance of the face is most characteristic. The cheeks become sunken, the eyes deeply set, the malar eminences prominent, the temporal regions sunken. When the patient smiles, the cheek is thrown into deep folds and the face generally has a cadaverous appearance. The neck becomes thin, the clavicles and scapulae extend prominently forward. The intercostal spaces are well marked; the breasts are pendulous and, owing to the disappearance of the fat, hard and nodular.

In contrast to this wasted appearance of the upper extremities and face, below the line of the iliac crests the individual presents a plump appearance; in some of the reported cases, even amounting to grotesqueness.

Usually, the attention of the family is first called to this condition by the emaciation which takes place in the face, and the fear of some

* Submitted for publication Aug. 4, 1917.

1. Simons, Arthur: Ztschr. f. d. ges. Neurol. u. Psychiat., Berlin, 1911 (Originalien).

2. Herrman, Charles: Progressive Lipodystrophy, THE ARCHIVES INT. MED., 1916, **17**, 516.

3. Webber, F. Parks: Quart. Jour. Med., 1916-1917, Nos. 37 and 38, p. 131.

disease prompts them to seek medical advice. The patients themselves complain little or not at all. In the advanced cases, there is sometimes a complaint of a feeling of chilliness and excessive perspiration; in other cases, a weakness or nervousness.

Fig. 1.—Author's patient at the age of 5.

The condition, in all reported cases, progresses for a certain time and then seems to be arrested. The ages, in reported cases, vary from 6 or 8 years to 39, the latter being the case of M. Laignel-Lavastine and Viard.[4]

Fig. 2.—Author's patient at the age of 8.

In all the cases there is a gradual progression of the emaciation of the face, upper extremities and trunk and increase in size of the lower extremities over a period of ten to twenty years, after which there is spontaneous arrest.

4. Laignel-Lavastine and Viard: Nouv. iconog. de la Salpétriére, 1912, **25,** 473 (with plate).

In the two cases reported by J. Husler[5] which occurred in males beginning in early childhood, there was no corresponding increase in the size of the lower extremities. It seems to be the opinion of most of those who have reported these cases that this increase in the deposit of fat in the pelvic region and lower extremities is rather a characteristic of the female sex. It is my opinion that this characteristic is accentuated by the efforts made to overnourish the patient to counteract the wasting which takes place in the upper portion of the trunk, face, etc.

Much speculation has resulted as to the cause of the condition: one author regarding it as secondary to tuberculosis; others as being the result of abnormal functioning of the sympathetic system. Most authorities think there is some relationship between this condition and

Fig. 3.—Author's patient at the age of 10.

abnormal functioning of the endocrine glands. It would, however, appear to me that this condition is closely related to the muscular dystrophies; that here one deals with dystrophy of fat tissue and in the latter, a dystrophy of muscle tissue. If this be the case, we are dealing with an abiotrophy. The condition does not seem to influence the duration of life. Examination of the skin and subcutaneous tissue in the emaciated areas shows the only pathologic change that has taken place to be an almost complete disappearance of fat.

Microscopically, traces of fat are found in the sebaceous glands and around the hair roots. In Simons' article[6] there are most excellent illustrations in which there is a comparison made between the sections of skin taken from the patient suffering from lipodystrophia progressiva and a markedly emaciated patient suffering with tuberculosis.

5. Husler, J.: Ztschr. f. Kinderh., 1914, **10,** 116.
6. Simons, Arthur: Ztschr. f. d. ges. Neurol. u. Psychiat., 1913, **19,** 377.

These illustrations show very clearly that even in the most emaciated individual there still remains some fat which can be readily demonstrated microscopically beneath the skin; whereas in a patient with lipodystrophia progressiva, there is practically an entire disappearance of fat in this same region.

Lipodystrophia progressiva must be differentiated from emaciation due to diseased conditions, such as tuberculosis, cancer, intestinal disease, nephritis, cardiovascular diseases, etc. This can readily be done by proper examination. It must be differentiated from facial hemiatrophy; from the emaciation that may occur in hyperthyroidism, at puberty, in the period of lactation, the menopause, etc.

Fig. 4.—Front and profile face views of author's patient.

Usually, if this condition is thought of and proper examination made, there is little difficulty in its diagnosis. The condition is slowly progressive and is limited to the fatty tissue of the face, neck, upper extremities and trunk; the muscles, bones, skin, vascular system, etc., not being affected.

The outlook as to life in these cases is extremely good; death, when it occurs, being due to some intercurrent condition. The condition usually advances for a number of years and then there is a spontaneous arrest. It does not interfere with the functional capability of the various organs or with physical or intellectual activity.

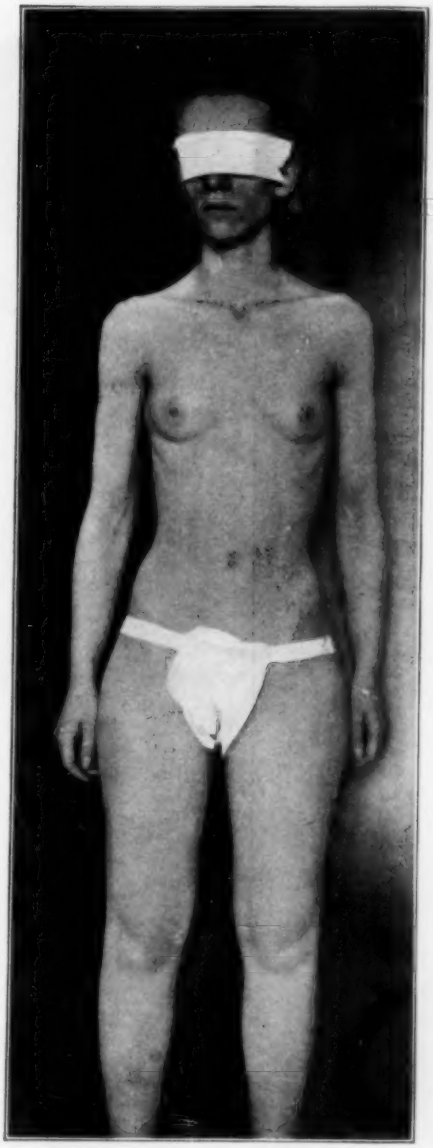


Fig. 5.—Front view showing emaciation of face, trunk and arms, and plump condition of hips, thighs and legs.

Fig. 6.—Lateral view of author's patient.

Fig. 7.—Back view.

The case reported by Herrman[2] existed for many years. The patient married and had several healthy children. Apparently, the chief objection to the condition is a cosmetic one. In the first case reported by Simons[1] the condition occurred in a dancer, and owing to the marring of her facial attractiveness, it interfered with her livelihood.

All sorts of treatments have been tried: the administration of the various glandular extracts, massage, electricity, tonics, overfeeding, hydrotherapy, etc. It would seem as if they were of but little use in allaying the progress of the condition. After a time, there occurred a spontaneous arrest. For cosmetic purposes, the injection of paraffin, fats and the transplantation of fat have been employed (Hollander[7]).

REPORT OF A CASE

The patient, T. M., aged 15, a schoolgirl, was seen in consultation with Dr. R. Tunstall Taylor, and examined in May, 1917.

The patient has the facial appearance of a very much older woman. She complains of a change in her facial appearance which has been progressive during six or seven years, her face growing thinner and thinner. Her shoulders, upper arms, chest and trunk have also become thinner, whereas her hips and legs have become fatter. These changes have been slowly but gradually progressing, as far as she and her mother can recall, for the past six or seven years.

Family History.—The father, aged 43, is healthy, not nervous. One paternal uncle is very nervous. Her mother, aged 39, is healthy, and very nervous. The patient has two brothers aged 9 and 12 years, and one sister aged 14. The brother aged 9, has epileptiform seizures of recent occurrence. The other brother and sister are healthy. There is no history of tuberculosis, cancer or chronic disease.

Past History.—The patient is the oldest child in the family. Her birth was normal. Following the birth of this child, the mother developed septicemia and was very ill, and this child was artificially fed; had gastric disturbances until the milk was properly modified. She teethed and walked at the normal time. At the age of 4 years the child had adenoids removed; at the age of 8, had scarlet fever accompanied by discharge from both ears. Between the eighth and ninth year she was operated on, having tonsils and adenoids removed. At the age of 9 years she first attended school. At the age of 10 years, she had whooping cough and at the age of 12 had measles. There is no history of trauma. Habits of living and diet are especially good.

Menstrual History.—Menstruation started at the age of 11; is regular, formerly painless, but lately there is some pain connected with the function.

Present Illness.—Between the eighth and ninth years the mother first noticed that the child's face and neck were thin, for which she gave her a tonic, and as she did not improve, she was taken to a physician who advised a special diet. This was carried out for about one year. Despite this, the wasting of the face continued. Gradually this wasting was noticed in the shoulders, arms, chest, back and abdomen. At the same time it was observed that the hips, thighs and legs were large and plump. There are absolutely no other complaints. The patient is athletically inclined and popular with her companions. Her appetite is good. She is happy, more or less constantly busy.

---

7. Hollander, Eugen: München. med. Wchnschr., 1910, **57**, 1794.

has no aches or complaints, sleeps well, and if it were not for the appearance of her face, would be perfectly contented.

Physical Examination.—Height, May 13, 1917, 4 feet 11¾ inches; weight, 90 pounds without clothes.

Measurements.—Biceps, right, 8 inches, left, 8¾ inches; forearm, right, 9 inches, left 8¾ inches; wrist, right, 6 inches, left, 6¼ inches; thigh, right, 19⅜ inches, left, 19⅛ inches; calf, right, 12⅝ inches, left, 12⅝ inches; ankle, right, 7⅝ inches, left, 7⅝ inches; chest over mammary glands, 28⅝ inches; chest below mammary glands, 26 inches; waist, 23 inches; around crest of ilium, 23⅝ inches; over anterior-superior spine, 26¼ inches; buttocks (greatest dimension), 33⅜ inches.

The patient's face presents the appearance of a very emaciated, middle-aged woman, without being wrinkled. The eyes are sunken; cheeks and temple fossae hollow; neck thin, with muscles standing forth prominently. When she smiles deep folds form around the angles of the mouth running upward toward the zygomas. On palpating a fold of the skin in her cheek one is immediately impressed with its extreme thinness. The facial appearance is almost cadaverous.

The chest walls show well marked intercostal spaces. The shoulders are angular, with bony prominences on the clavicles, and the scapulae well defined. The spinous processes of the vertebral bodies extend prominently forth. The breasts are slightly pendulous and somewhat nodular. The axillary and pubic hair is well defined.

Below the iliac crests, the patient presents a quite different appearance. The buttocks are large and covered with a thick layer of fat; the thighs are large, well rounded with the development of much subcutaneous fat. The knees are dimpled and the calves of the legs large.

The skin is soft, elastic and of normal color, except on the face, where it appears paler than normal. There are no scars, indurations, etc. The skeleton is normally developed. Roentgen-ray examination of the skull, spine and upper extremities reveals no abnormalities. The joints are everywhere freely movable.

The head is well formed, ears set well, eyes set far back in the orbits. The tongue is clean, protruded in the midline. The patient has several teeth in bad condition, but this has been of very recent occurrence—within the past six months.

Chest.—Examination of the heart and lungs reveals absolutely nothing pathologic. Examination of the abdomen is negative, with the exception of a slight increase in the liver dulness, which extends one inch below the costal margin. The splenic dulness is also slightly increased.

Roentgenographic and fluoroscopic examination of the stomach shows it to be of the fish-hook type, prolapsed below the crest of the ilium in the upright position. The stomach, at the time of the examination, was actively contracting; emptying itself in three hours; the hepatic flexure of the colon is prolapsed, the first portion of the transverse colon being persistently fixed in the cecal region. There is a marked twenty-four-hour stasis. There is gastroptosis and enteroptosis. (Dr. Walton, roentgenographer.)

Eye, Ear, Nose and Throat Examination.—There is slight retraction of both eyelids. Convergence is normal; eye motions are normal; extra-ocular structures are normal. The pupils are active and equal. The fundi and fields are normal. Vision, right, 15/9; left, 15/9. Both eyes are emmetropic.

The nasal examination was negative.

Both ear drums are normal. Hearing for the tuning fork is normal. Large piece of tonsil tissue on the left side, and a fairly large sized mass on the right side. (Dr. William Tarrun.)

Urine: Single specimen, specific gravity 1.011. It is light yellow, clear, acid, with a faint trace of albumin. Sugar and blood are negative. Microscopically there are many epithelial cells, with an occasional white blood cell. There are no casts or red blood cells. A twenty-four hour specimen comprised

470 c.c. Specific gravity, 1.014; urea, 9.75 gm.; chlorids, 5 gm. Otherwise negative.

Blood: May 9, 1917. The Wassermann blood test was negative; hemoglobin, 90 per cent.; leukocytes, 8,000; red blood cells, 4,320,000. Polymorphonuclears, 54 per cent.; small lymphocytes, 25 per cent.; large lymphocytes, 15 per cent.; eosinophils, 2 per cent.; large mononuclears, 3 per cent.; transitionals, 1 per cent.

Sputum: None obtained.

Stomach contents: A double test meal given at 7 and 11 a. m. and drawn at 12 shows much undigested material, especially egg yolk and starch granules. Free hydrochloric acid, 24 degrees; total acidity, 68 degrees; blood and bile negative.

Stool: Clay colored. Bile and blood are absent. There is an abundance of free fat present. Otherwise negative.

Renal function: Phenolsulphonephthalein, first hour, 151 c.c., 69 per cent.; second hour, 40 c.c., 9 per cent.

Blood Pressure: Systolic, 105; diastolic, 55.

Sugar Tolerance: May 12, 1917, 150 gm. given without appearance in the urine. May 13, 1917, 200 gm. given without appearance in the urine.

Pelvic Examination: Special examination was not made.

Neurologic Examination: Motor function, muscle power, tone and volume are normal.

Owing to the fact that this young woman is athletically inclined, there is remarkably good development and strength of her muscles. The muscles in the upper extremities, shoulders and neck all stand forth prominently. There are no abnormal movements; electrical reactions are normal. Coordination of the upper and lower extremities, normal.

Reflexes: All tendon reflexes are slightly increased. The superficial reflexes are all about normal. The Babinski reflex is absent.

Sensory Functions: There is absolutely no disturbance of sensation in any of its qualities. The stereognostic sense is normal.

Vasomotor System: Nothing abnormal was noted.

Trophic Function: There is marked absence of subcutaneous fat in the face, neck, shoulders, arms, chest, abdomen and back; also a marked increase in the subcutaneous fat in the buttocks, thighs, calves and legs.

The organic reflexes are normal.

Mental Examination.—This shows an exceptionally intelligent young girl, who is quick and alert but somewhat emotional, inclined to be moody and rather sensitive. She sleeps rather lightly and is easily disturbed during the night.

CONCLUSION

The various diseases which might occasion wasting and those diseases in which atrophy of the bone, muscle, etc., occur were taken into consideration and in the absence of physical signs and symptoms they were excluded and a diagnosis of lipodystrophia progressiva was arrived at.

1810 Madison Avenue.

THE EFFECT OF VARIOUS NEUTRAL SOLUTIONS ON GASTRIC DISCHARGE, GASTRIC SECRETION AND DUODENAL REGURGITATION *

W. E. MORSE, A.B., M.D.
CHICAGO

In a recent publication[1] attention was called to various conflicting experimental and clinical observations concerning the relation of acidity of gastric contents to the rate of gastric discharge. In general, physiologic literature supports the theory that an acid reaction is essential to and hastens gastric discharge up to an optimum acidity of from 0.15 to 0.25 per cent. Some clinical observers find that so-called hyperacidity increases gastric motility, while others consider it a contributing factor in stasis and gastric dilatation. Motility is often unimpaired in cases of achylia gastrica. Our investigations showed: (1) that water is discharged from the fasting stomach of anesthetized pithed dogs more rapidly than any percentage of acid; (2) the rate of discharge is decreased with increase of acidity; (3) duodenal regurgitation as evidenced by increase in the contents of the stomach often occurred at 0.2 per cent. acidity, and in nearly all trials occurred at or before 0.3 per cent. acidity was reached; (4) increase in acidity augments the frequency and amount of regurgitation from the duodenum. Similarly, Spencer, Meyer, Rehfuss and Hawk[2] observed that 1.0 per cent. sodium bicarbonate solution hastened the discharge from the normal human stomach, while 5.0 per cent. solution delayed it.

Considering these various observations, Dr. Hoskins suggested the possibility that the mechanism of gastric discharge might respond to stimulation by other substances than acid; that is, the control of the pylorus might be merely a nonspecific phase of the so-called "law of the gastro-intestinal tract," with a local reversal of direction at the pyloric segment when stimulation on the gastric side is supranormal. If this theory were true it would follow that stimulating solutions other than acid, in low concentration, should hasten discharge from the stomach, while high concentrations would produce a regurgitation from the duodenum into the stomach.

To test this hypothesis and to secure data concerning the effect of varying chemical conditions in the stomach on gastric secretion and

* Submitted for publication July 10, 1917.

* From the Laboratory of Physiology of the Northwestern University Medical School.

1. Morse, W. E.: Am. Jour. Physiol., 1916, **41**, 439.
2. Spencer, Meyer, Rehfuss and Hawk: Am. Jour. Physiol., 1916, **39**, 462.

duodenal regurgitation, several series of experiments were undertaken, using different concentrations of neutral solutions.

The conditions imposed were identical with those of the acid series previously reported,[1] namely, first, a normal fasting stomach; second, fluid injections of constant temperature and quantity, but of varying concentrations; third, abolishment of inhibitory reflexes by pithing the spinal cord or sectioning the splanchnic nerve; and fourth, general ether anesthesia. As a check on the foregoing, parallel experiments were made on animals with the pylorus ligated in order to eliminate any errors in the calculation of the rate of discharge from the stomach which might arise from the secretion of an unknown quantity of gastric juice.

TECHNIC

There was no change in method from that used in the series of experiments previously reported.[1] Ether anesthesia was maintained by the tracheal cannula-ether bottle method. Through a laminectomy incision the spinal cord was destroyed from the sixth to the tenth dorsal segments, or the splanchnic nerves were sectioned above the diaphragm by opening the thorax laterally between the ninth and tenth ribs, while maintaining respiration by a Gesell apparatus. Fluids were injected into and withdrawn from the stomach by means of a glass tube inserted through an esophageal fistula, opening just above the sternum. Injections were made at intervals of one half hour and the amount of discharge or of regurgitation was computed by noting the difference between the amount of fluid injected and the amount withdrawn. The animals were not fed during the twenty-four hours preceding the operation, and in every case the efficiency of the aspirating technic was tested by a preliminary gastric lavage, and by a postmortem examination of the gastric contents. In all cases the solutions injected were titrated, before injection and after aspiration, with phenolphthalein as indicator, to determine the change of acidity during the thirty minute intervals the fluids remained in the stomach.

Seven series of experiments were completed consisting of two sodium chlorid, two sodium acetate, one tabasco pepper sauce, one repeated water injection, and an extension of experiments, previously referred to, with hydrochloric acid injections into the stomach after ligation of the pylorus.

Sodium Chlorid Solutions.—The concentrations of solutions used varied from 0 to 10 per cent., and injections were made at thirty minute intervals. In Series 1 eight animals were used. The cord was pithed in the first six; in the last two the splanchnics were cut. In Series 2 six animals were used and the pylorus was ligated. This series was made as a check on Series 1 to determine the amount of absorption of fluids from the stomach, of secretion of fluids into the stomach, or of accumulation of fluid from osmosis, since these factors, if unknown, would render unreliable any computation as to rate of discharge from the stomach, or regurgitation of fluids from the duodenum. The inhibitory mechanism was not blocked in Series 2, for it was observed in the series of continuous water injections (Table 6) that secretion as determined by acid titration was not materially altered by section of the splanchnic nerves.

The results from injection of sodium chlorid solutions into the stomach are shown in Tables 1 and 2. The rate of discharge as shown in Table 1 apparently is decreased with increase of the concentration of the solution. When we consider the increase in the gastric contents with the various solutions, however, when the pylorus is ligated, as shown in Table 2, we find there is more increase for the same solutions with the pylorus closed. Thus

TABLE 1.—Discharge and Secretion with Solutions of Sodium Chlorid

Dog No.	H_2O			NaCl 1%			NaCl 3%			NaCl 5%			NaCl 7%			NaCl 10%			H_2O		
	D	I	HCl	D	I	HCl	D	I	HCl	D	I	HCl	D	I	HCl	D	I	HCl	D	I	HCl
1†	20	0	4.0	30	0	2.0	10.0	0	2.0	0	0	2.0	50*	0	2.0	0	0	2.5	0	0	2.0
2†	12	0	3.0	5	0	2.0	0	5.0	2.0	0	15.0	2.5	0	20.0	2.5	0	10.0	2.5	8	0	1.0
3†	5	0	1.0	5	0	1.0	2.0	0	1.5	0	10.0	1.5	0	5.0	1.5	0	15.0	2.0	0	0	2.0
4†	5	0	1.0	5	0	1.0	0	5.0	1.0	0	0	1.0	0	0	1.0	0	25.0	1.0	0	0	§
5†	10	0	2.0	0	10.0	1.0	0	20.0	2.0	0	10.0	1.5	0	30.0	2.0	0	30.0	2.0	0	10	1.0
6†	5	0	1.5	0	0	1.5	0	0	1.0	0	15.0	1.0	0	15.0	1.0	0	5.0	1.0	0	5	1.0
7‡	15	0	1.2	5	0	1.4	15.0	0	1.4	0	40.0	1.5	0	20.0	1.5	0	15.0	1.5	§	§	§
8‡	6	0	1.4	8	0	1.5	8.0	0	1.7	5	0	1.6	0	7.0	1.2	0	15.0	1.4	0	0	1.4
Average	9.7	0	1.9	7.2	1.25	1.4	4.4	3.75	1.57	0.6	11.25	1.58	0	12.1	1.58	0	14.4	1.7	1	2	1.4

D = decrease of fluids in the stomach.
I = increase of fluids in the stomach.
HCl = hydrochloric acid expressed in terms of tenth-normal acidity per 100 c.c. of fluid aspirated.
* = unusual occurrence not included in the average.
§ = not determined.
† = cord pithed.
‡ = splanchnic cut.

TABLE 2.—Secretion with Sodium Chlorid Solutions. Pylorus Ligated

Dog No.	H_2O			NaCl 1%			NaCl 3%			NaCl 5%			NaCl 7%			NaCl 10%		
	A	I	HCl	A	I	HCl	A	I	HCl	A	I	HCl	A	I	HCl	A	I	HCl
1	0	0	2.0	2.0	0	2.0	0	0	1.5	0	15.0	1.0	0	20.0	2.0	0	18.0	2.0
2	6.0	0	1.0	0.0	4.0	1.0	0	0	1.2	0	18.0	1.0	0	14.0	1.6	0	16.0	1.2
3	0	0	1.0	0.0	0	0.6	0	10	0.8	0	15.0	1.0	0	23.0	1.3	0	65.0	1.8
4	5.0	0	1.7	4.0	0	1.0	0	0	1.0	0	20.0	1.2	0	35.0	1.2	0	18.0	1.6
5	5.0	0	1.0	8.0	0	1.0	0	5	1.0	0	0	1.0	0	45.0	1.2	0	30.0	1.5
6	10.0	0	1.2	5.0	0	1.2	0	15	1.2	0	35.0	1.7	0	35.0	1.9	0	35.0	2.2
Av.	4.83	0	1.31	3.1	0.66	1.13	0	5	1.1	0	17.1	1.15	0	28.66	1.5	0	30.0	1.7

A = absorption.
I = increase of fluids in the stomach.
HCl = hydrochloric acid expressed in terms of tenth-normal acidity per 100 c.c. of fluid.

for 5 per cent. solutions, with the pylorus open we have an average increase of 11.25 c.c., while with the pylorus ligated the increase is 17.1 c.c., leaving an excess of 6.15 c.c. which represents discharge. Also the excess with the pylorus ligated over the amount of increase with patent pylorus, is 16.55 c.c. for 7 per cent. solutions and 15.9 c.c. for 10 per cent. solutions. This indicates an increase rather than a decrease in the rate of discharge.

The increase in the contents of the stomach with high concentrations of sodium chlorid solutions both with the pylorus closed and with it open is supposedly due largely to osmosis. Secretion, however, contributes a small part to the aggregate amount. This is shown by the fact that the total acidity remained fairly constant with both open and closed pylorus, hence the secretion of acid was not accelerated by the presence of the solution or increase in concentration. The amount of acid secreted in the thirty minute intervals varied from 1.4 to 1.7 c.c. tenth-normal acidity per 100 c.c. Taking the average increase in acidity as 1.58 c.c. of tenth-normal hydrochloric acid per 100 c.c., this would give 3.18 c.c. of tenth-normal acid for the total 200 c.c. of fluid aspirated. Considering the acidity of the gastric juice as 0.5 per cent., as demonstrated by Heidenhain,[3] Pawlow,[4] Sommerfeld,[5] Carlson,[6] and others, this would give an equivalent of 2.7 c.c. of gastric juice. It is therefore evident that the contribution of secretion to the increase of fluid is small.

Regurgitation also is excluded by the fact that the increase was greater when the pylorus was closed than when open. Presence of bile was never observed, but the amount of mucus increased with increase in concentration.

Some individual variations are noted, the most pronounced of which is found in Animal 1, Table 1, which showed rather larger discharge than usual; these were associated with liquid bowel movements and at necropsy the gastric mucosa was hemorrhagic. The large discharge obtained in the case with 7 per cent. solution was so unusual that it was eliminated from the averages.

Sodium Acetate Solutions, Series 3.—Ten dogs were used in this series and in all cases the splanchnic nerves were cut. The concentrations used varied from 0 to 10 per cent. In the first four experiments, solutions of acetate gradually increasing to 10 per cent. were employed. In the last six only water and 10 per cent. solution were injected, after which the pylorus was ligated and the animals transferred to Series 4. This latter is the companion series, being utilized as a check on the secretory or osmotic factors involved. Seven animals were used in Series 4, of which only the first was independent of Series 3. By study of the results of the first four animals of Series 3 and the first animal of Series 4 it was surmised that the work could be expedited without materially reducing the value of the data by testing first the discharge of water and 10 per cent. sodium acetate, and then after ligation of the pylorus, testing the secretion or osmosis with the same concentration of solutions on each animal. Thus, Experiment 2 of Series 4 is continuous with Experiment 5 of Series 3, and the others following in consecutive order.

The results are shown in Tables 3 and 4. There is a decrease in discharge with increase in concentration, as shown by the results in Table 3. There is also an increase in the fluid contents of the stomach, with increase in concentration, and the average increase is the same for 10 per cent. concentration with the pylorus open and closed. This would indicate that the rate of discharge is decreased from an average of 12.2 c.c. with water to 0 with 10 per cent. acetate. The amounts of increase both with the pylorus open and closed is less with acetate than with the chlorid, and the amount of mucus was less. Bile was never observed. The increase in acidity is fairly constant both for

3. Heidenhain: Arch. f. d. ges. Physiol., 1872, **19,** 153.
4. Pawlow: Work of the Digestive Glands (Trans. W. H. Thompson), London, 1910, p. 32.
5. Sommerfeld: Arch. f. Anat. u. Physiol., Suppl., 1905, p. 455.
6. Carlson: Am. Jour. Physiol., 1915, **38,** 258.

TABLE 3.—Discharge and Secretion with Solutions of Sodium Acetate

Dog No.	H_2O			Sodium Acetate 0.5%			Sodium Acetate 1%			Sodium Acetate 3%			Sodium Acetate 5%			Sodium Acetate 10%			H_2O		
	D	I	HCl	D	I	HCl	D	I	HCl	D	I	HCl	D	I	HCl	D	I	HCl	D	I	HCl
1	12.0	0	1.0	7.0	0	2.0	7.0	0	2.0	0	9	3.0	0	0	3.0	0	12.0	2.5	0	5.0	1.0
2	10.0	0	3.0	25.0	0	2.5	0	10	3.5	0	5.6	3.5	0	0	4.0	0	5.0	4.0	8	0	2.5
3	15.0	0	2.5	10.0	0	2.5	10.0	0	2.5	0	5.0	3.0	0	10.0	3.0	0	3.0	2.5	0	0	1.5
4	0	0	2.0	5.0	0	1.5	5.0	0	1.0	5.0	0	1.5	0	5.0	1.5	0	13.0	2.0	0	10.0	0.5
5	20.0	0	1.6	.....	.....	.....	.....	.....	.....	....	...	.....	...	.....	.....	0	5.0	1.6			
6	0	0	2.0	.....	.....	.....	.....	.....	.....	....	...	...	..	.....	.....	0	0	1.6			
7	15.0	0	1.6	.....	.....	.....	.....	.....	.....	.....	...	...	..	.....	.....	0	6.0	2.4			
8	15.0	0	1.6	.....	.....	.....	.....	.....	.....	....	....	.....	...	.....	.....	0	10.0	7.7			
9	30.0	0	1.6	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	.....	.....	0	10.0	2.0			
10	5.0	0	3.6	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	.....	.....	0	5.0	4.4			
Average	12.2	0	2.06	11.75	0	2.1	5.5	2.5	2.25	1.25	2.5	2.75	0	4.5	2.88	0	6.9	3.07	2	3.8	1.38

D = decrease of fluids in the stomach.
I = increase of fluids in the stomach.
HCl = hydrochloric acid expressed in terms of tenth-normal acidity per 100 c.c. of fluid.
The splanchnic nerves were sectioned in all cases.

TABLE 4.—Secretion with Solutions of Sodium Acetate. Pylorus Ligated

Dog No.	H_2O			Sodium Acetate 0.5%			Sodium Acetate 1%			Sodium Acetate 3%			Sodium Acetate 5%			Sodium Acetate 10%			H_2O		
	A	I	HCl	A	I	HCl	A	I	HCl	A	I	HCl	A	I	HCl	A	I	HCl	A	I	HCl
1	2	0	1.5	5	0	1.5	5	0	2.5	0	0	2.5	0	5	2.5	0	5.0	2.5	*	*	*
2	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	0	0	2.0	5.0	0	2.0
3	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	..	....	.....	.....	.....	0	12.0	2.0	0	15.0	2.0
4	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	0	2.0	1.6	0	11.0	2.0
5	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	0	5.0	2.0	0	18.0	2.4
6	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	0	20.0	1.2	0	20.0	1.6
7	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	....	.....	.....	.....	0	0	1.6	0	0	2.0
Average	.....	.....	.....	.....	.....	.....	.....	...	.....	.....	.....	.....	.....	.....	.....	0	6.29	1.8	0.8	10.66	2.0

* = not determined
D = decrease of fluids in the stomach.
I = increase of fluids in the stomach.
HCl = hydrochloric acid expressed in terms of tenth-normal acidity per 100 c.c. of fluid.
The splanchnic nerves were cut in all cases.

TABLE 5.—Discharge and Secretion with Tabasco Pepper Sauce

Dog No.	H_2O			Tabasco Pepper Sauce 15 C.c. to L.				H_2O			Tabasco Pepper Sauce 15 C.c. to L.		
	D	I	HCl	D	I	HCl		D	I	HCl	D	I	HCl
1	10.0	0	0.8	14.0	0	0.8	Pylorus Ligated	0	8.0	0.8	0	0	0.8
2	12.0	0	0.8	10.0	0	0.8		0	0	1.2	0	0	1.2
3	5.0	0	1.6	0	0	1.6		10.0	0	2.0	15.0	0	2.4
4	8.0	0	1.2	5.0	0	2.0		0	0	1.2	4.0	0	2.0
5	0	0	1.2	20.0	0	1.2		0	0	1.2	15.0	0	1.2
6	40.0	0	1.2	26.0	0	1.6		0	7.0	1.2	0	4.0	1.2
7	5.0	0	2.0	10.0	0	1.2		4.0	0	1.2	0	2.0	1.2
Average	12.2	0	1.25	12.1	0	1.3		2.0	2.1	1.56	4.1	0.9	1.4

D = decrease of fluids in the stomach.
I = increase of fluids in the stomach.
HCl = hydrochloric acid expressed in terms of tenth-normal acidity per 100 c.c.
In all cases the spinal cord was pithed.

water and all percentages of acetate used. Increase in the fluid content here also is attributed primarily to osmosis. We are unable to explain the high average of 10.66 c.c. increase in the gastric content with injections of water after ligation of the pylorus, and after the injection of 10 per cent. acetate, as shown in Table 4. It is possible that this increase is due to an exudation following irritation of the mucosa, although the mucosa at necropsy was not congested.

Solution of Tabasco Pepper Sauce.—Concentrations sufficient to produce a burning peppery taste were used, a result which was obtained with 15 c.c. of pepper sauce to the liter. Seven animals were used and in all cases the spinal cord was pithed. Two injections were made before and two after the ligation of the pylorus, giving the discharge and secretion rate of each animal as in Series 3 and 4. Water was first injected followed by the solution of pepper sauce. When discharge had been noted, after thirty minute intervals, for each solution the pylorus was ligated and the injections repeated to obtain data concerning secretion.

The results are given in Table 5. It is noted that there is practically no difference in the rate of discharge with water and with solutions of tabasco sauce. Also the secretion rate and acidity are practically unchanged.

Repeated Injections of Water.—Water was repeatedly injected in a series of ten animals. In the first five the splanchnic nerves were cut; in the last five, the inhibitory mechanism was left intact. In the first two animals the injections were repeated at thirty minute intervals; in the remaining cases the interval was one hour. These experiments were made to determine whether fatigue, continued narcosis or a progressive development of shock played a significant rôle in modifying the rate of discharge. The results are shown in Table 6. It is seen that the average rate of discharge is unchanged at the end of three hours and but slightly reduced at the end of five hours. The initial rate of discharge for each animal remains practically unchanged throughout the experiment, and the same is true for the amount of acid secreted. Also, there is practically no difference in discharge or acid secretion with the splanchnic nerves cut or intact.

TABLE 6.—Repeated Determinations of—

Splanchnics Cut

Dog Number	H_2O ½ Hour			H_2O 1 Hour			H_2O 1½ Hours			H_2O 2 Hours		
	D	R	HCl	D	R	HCl	D	R	HCl	D	R	HCl
1	10.0	0	5.6	13.0	0	2.2	10.0	0	2.0	5.0	0	1.6
2	15.0	0	1.2	12.0	0	0.8	6.0	0	0.8	11.0	0	0.8
3	.....	...	.....	10.0	0	1.0	.....	...	.....	5.0	0	1.2
4	.....	...	.....	0	0	1.0	.....	...	.....	4.0	0	1.0
5	.....	...	.....	5.0	0	1.0	.....	...	.....	12.0	0	0.6
Splanchnics Not Cut												
6	.....	...	.....	12.0	0	1.4	.....	...	.....	18.0	0	1.8
7	.....	...	.....	7.0	0	1.2	.....	...	.....	7.0	0	1.0
8	.....	...	.....	13.0	0	1.6	.....	...	.....	9.0	0	1.2
9	.....	...	.....	5.0	0	1.8	.....	...	.....	0	2.0	1.4
10	.....	...	.....	25.0	0	1.4	.....	...	.....	5.0	0	1.8
Average	12.5	0	3.4	10.2	0	1.4	8.0	0	1.4	7.6	0.2	1.24

D = discharge from the stomach.
R = regurgitation into the stomach.
HCl = hydrochloric acid expressed in terms of tenth-normal acidity per 100 c.c.

Injections of Hydrochloric Acid with the Pylorus Ligated.—This series is an extension of experiments previously reported.[1] It shows the effect of various concentrations of hydrochloric acid on gastric secretion. The animals were pithed and the pylorus ligated. The solutions varied from 0 to 0.5 per cent. The results as given in Table 7 show practically no secretion with any concentration except in one unusual case with 0.5 per cent. acid, in which 12 c.c. of secretion were obtained. The acidity of the solution injected is decreased during the thirty minute interval and the neutralization is greater for the higher percentages.

DISCUSSION

The solutions used in the experiments were chosen on the basis of nontoxicity, solubility and importance of the substances in dietetics or therapeutics.

Attention has previously been called[1] to the small discharge of water obtained under the conditions imposed in these experiments as compared with that obtained by Moritz[7] from duodenal fistulas. In the various experiments on gastric discharge performed in this laboratory a total of fifty-one dogs have been used. In each animal the rate of discharge of water was ascertained as a standard for comparison with the rate for various solutions. The average discharge of water from

7. Moritz: Ztschr. f. Biol., 1901, **42**, 584.

—THE RATE OF DISCHARGE OF WATER

Splanchnics Cut

H_2O 2½ Hours			H_2O–30ns 3 Hours			H_2O 3½ Hours			H_2O 4 Hours			H_2O 4½ Hours			H_2O 5 Hours		
D	R	HCl	D	R	HCl	D	R	HCl	D	R	HCl	D	R	HCl	D	R	HCl
12.0	0	1.6	5.0	0	1.6	11.0	0	1.6									
20.0	0	0.8	15.0	0	0.8	10.0	0	0.8									
.....	.....	.....	13.0	0	1.4	.....	.....	.....	5.0	0	1.2	.....	.....	.....	14.0	0	1.1
.....	.....	.....	6.0	0	1.0	.....	.....	.....	5.0	0	1.0	.....	.....	.....	10.0	0	1.0
.....	.....	.....	12.0	0	0.6	.....	.....	.....	0	0	0.6	.....	.....	.....	10.0	0	1.0

Splanchnics Not Cut

.....	.....	.....	25.0	0	1.4	.....	.....	.....	15.0	0	1.6						
.....	.....	.....	0	2.0	1.0	.....	.....	.....	5.0	0	1.0	.....	.....	.....	5.0	0	1.2
.....	.....	.....	10.0	0	1.2	.....	.....	.....	25.0	0	1.2	.....	.....	.....	0	0	1.2
.....	.....	.....	5.0	0	1.8	.....	.....	.....	5.0	0	1.4	.....	.....	.....	5.0	0	1.4
.....	.....	.....	15.0	0	1.0	.....	.....	.....	0	3	1.0	.....	.....	.....	15.0	0	1.2
16.0	0	1.2	10.6	0.2	1.18	10.5	0	1.2	7.5	0.4	1.1	.....	.....	.....	7.4	0	1.0

these fifty-one animals was 14.3 c.c. in thirty minutes. Of these fifty-one individuals, six had a discharge exceeding 25 c.c., while five animals showed no discharge. If these extreme cases are eliminated, we have forty which show within a narrow margin of deviation an average discharge of 10 c.c. per half hour. It is hoped that future observations will determine what conditions are responsible for this relatively slow rate. It is possible that general ether anesthesia or the presence of a tube in the cardiac orifice of the stomach may be significant factors. As previously noted,[1] Cannon[8] determined that section of the splanchnic nerves in cats resulted in no change of the normal movements of any part of the alimentary canal, and Carlson[9] found that section of the splanchnics in dogs increased the gastric tonus and augmented gastric hunger contractions. This eliminates the possibility that destruction of the inhibitory mechanism is the significant factor.

Pawlow[10] found that gastric secretion is only slightly stimulated by the introduction of water into the stomach, and that solutions of meat ash, chlorid and hydrochloric acid produced the same results as water alone. Throughout these experiments small but constant amounts of acid have been noted. Titration for total acidity, using phenolphthalein

8. Cannon: Am. Jour. Physiol., 1906, **17**, 431.
9. Carlson: Am. Jour. Physiol., 1913, **32**, 382.
10. Pawlow: Am. Jour. Physiol., 1913, **32**, 112.

as indicator, was made after each aspiration. The notations in the tables are in terms of tenth-normal acidity per 100 c.c. As the total gastric contents were 200 c.c., this represents half of the total acid secreted in the thirty minutes that the fluid remained in the stomach. By computing the amount of gastric juice from the acid present it is found that in thirty-five animals the rate of secretion per thirty minutes in the presence of water varies with few exceptions from 1.4 c.c. to 5.6 c.c., with an average of 2.33 c.c. The injection of other solutions as sodium chlorid, sodium acetate and tabasco sauce does not materially change this rate. The average secretion for sodium chlorid is 2.27 c.c., for sodium acetate 3.3 c.c., and for tabasco pepper sauce 2 c.c. Hydrochloric acid also produces no essential change in the rate of secretion

TABLE 7.—Secretion with Solutions of Hydrochloric Acid. Pylorus Ligated

Dog No.	H_2O			HCl 0.1%			HCl 0.2%			HCl 0.3%			HCl 0.4%			HCl 0.5%		
	A	S	HCl	A	S	HCl	A	S	HCl	A	S	HCl	A	S	HCl	A	S	HCl
1	0	0	1.6	0	4	−3.6	0	1	−6.0	0	0	−11.6	0	0	−16.8	0	12.0*	−19.6
2	0	0	2.0	0	0	−4.0	0	0	−7.2	0	0	−10.0	0	3	−16.0	0	5.0	−16.0
3	15.0	0	2.0	0	0	−2.0	0	0	−5.6	0	0	−8.0	0	0	−6.0	0	0.0	−10.0
4	5.0	0	1.4	0	0	−2.0	5.0	0	−6.0	0	0	−10.0	0	0	−15.0	0	0.0	−17.0
5	5.0	0	1.8	0	0	−2.0	5.0	0	−2.8	5	0	−4.8	0	0	−5.2	0	5.0	−13.2
6	7.0	0	2.0	0	0	−3.2	0	0	−4.0	0	2	−6.0	0	0	−10.0	0	0.0	−12.0
Av.	5.2	0	1.8	0	0.66	−2.8	1.66	0.17	−5.25	0.83	0.33	−8.4	0	0.5	−11.5	0	3.66	−14.6

* = unusual result. The cord was pithed in all cases.
A = absorption from the stomach.
S = secretion into the stomach.
HCl = hydrochloric acid expressed in terms of tenth-normal acidity per 100 c.c. of fluid. Minus sign indicates decrease in acidity.

as shown by the data in Table 7. Here, with the pylorus ligated, the average increase in the gastric contents varies from 0 with water to 3.66 c.c. with 0.5 per cent. hydrochloric acid. The high average obtained with 0.5 per cent. hydrochloric acid solution is largely due to one unusual result of 12 c.c. increase. With all other percentages of acid used the average increase was less than 1 c.c. These findings are corroborative of the observations of Pawlow.[10]

Carlson[11] observed that the gastric glands of the human stomach are never quiescent, but continue to secrete from 2 c.c. to 50 c.c. per hour. The results obtained in these experiments show the rate of secretion for the dog's stomach under the conditions specified approximates the minimum for the human stomach in the nonactive state.

11. Carlson: Am. Jour. Physiol., 1915, **37**, 50.

Rehfuss and Hawk[12] have presented direct evidence of the secretion of gastric juice of constant acid concentration by the human stomach. In our experiments, continued presence of a fairly constant amount of acid in the total gastric contents, as determined at thirty minute intervals, also indicates that the rate of secretion of acid is constant for a given stimulus.

The data obtained from injection of hydrochloric acid solution into the stomach after ligation of the pylorus are shown in Table 7. This series is an extension of experiments[1] referred to as evidence that secretion is not a disturbing factor in computing the rate of gastric discharge with acid solutions. In addition to the evidence they afford as to the amount of secretion in the presence of hydrochloric acid solutions, the observations indicate that there is probably a neutralizing substance in the gastric secretions which increases with increased acid concentration in the stomach contents. With 0.1 per cent. hydrochloric acid there is a decrease in the acidity of the solution which varies from 2 to 4 c.c. of tenth-normal acidity per 100 c.c., with an average of 2.8 c.c. This decrease is larger for each higher acid concentration until an average neutralization of 14.6 is reached with 0.5 per cent. hydrochloric acid. As the titrations were made for total acidity with phenolphthalein indicator, this decreased acidity cannot be attributed to combination of the acid with mucus. Slight hemorrhage into the stomach was frequently present, but by color comparison with a solution of known hemoglobin content it was estimated that these hemorrhages would not exceed 2 c.c., which could not account for the amount of the progressive increase in the extent of the neutralization. No tests were made for the presence of ammonia, hence it cannot be asserted that this was the factor producing the decrease in acidity, but since ammonia has been demonstrated in the gastric contents by numerous investigators, as tabulated by Huber,[13] and in the pure gastric juice by Strauss[14] and Carlson,[15] it must be considered a factor in the neutralization of the acid, and in the absence of other demonstrable sources of neutralization it is probably the principal factor. Huber[16] finds that the amount of ammonia has no relation to the concentration of acid or pepsin. As previously noted in our experiments, the amount of neutralization is proportional to the concentration of the acid. However, the ether anesthetic might be a factor in stimulating the liberation of ammonia which Huber[17] finds to have a complex origin, repre-

12. Rehfuss and Hawk: Gastro-Intestinal Studies, Jour. Am. Med. Assn., 1914, **63,** 2088.
13. Huber: Am. Jour. Physiol., 1917, **42,** 405.
14. Strauss: Berl. klin. Wchnschr., 1893, **30,** 398.
15. Carlson: Am. Jour. Physiol., 1915, **38,** 248.
16. Huber: Am. Jour. Physiol., 1915, **38,** 418.
17. Huber: Am. Jour. Physiol., 1915, **38,** 419.

senting excretion from the blood, deamidization in the gastric mucosa, or possibly the action of gastric flora. In our experiments the gastric flora is eliminated as a possible factor by the acid concentration of the solutions used, the limited time interval and the frequent lavage produced by repeated aspirations.

The possibility has also to be considered that the decrease in acidity might have been due, not to neutralization, but to resorption of the acid.

SUMMARY

1. Solutions of sodium chlorid varying from 1 to 10 per cent. slightly augment the rate of discharge of fluids from the stomach of anesthetized and pithed or splanchnicotomized dogs. Solutions of concentration above 3 per cent. produced an increase of fluid in the stomach by osmosis, but with the pylorus ligated the increase exceeded that obtained with the pylorus patent, sufficient to indicate a discharge greater than the discharge with water.

2. Solutions of sodium acetate slightly retard the discharge of fluid from the stomach of anesthetized and splanchnicotomized dogs.

3. The fluid content of the stomach is usually increased when solutions of sodium chlorid or sodium acetate are injected in concentration above 3 per cent. This increase is attributed to osmosis exceeding the amount of discharge.

4. The rate of secretion of gastric juice as computed from the increase of acidity averages 2.33 c.c. per thirty minutes, when water is injected into the stomach and the pylorus is patent. This rate of secretion is not materially altered by ligation of the pylorus or injection of solutions of sodium chlorid, sodium acetate or tabasco pepper sauce.

5. The acidity of solutions of hydrochloric acid injected into the stomach of anesthetized dogs with pylorus ligated is decreased, the rate of diminution increasing with increase in the acidity of the solutions.

6. The average discharge of water from the stomach was 14.3 c.c. per thirty minutes in fifty-one trials. By eliminating eleven extreme cases the average for forty animals is reduced to 10 c.c.

7. Solutions of tabasco pepper sauce are discharged from the stomach at practically the same rate as water.

8. The mechanism of gastric discharge does not react to solutions of sodium chlorid, sodium acetate and tabasco pepper sauce, in the same manner that it reacts to solutions of hydrochloric acid.

I wish to express my gratitude for the many helpful suggestions given by Dr. R. G. Hoskins in connection with this work.

A SIMPLE TECHNIC FOR THE DEMONSTRATION OF A PHAGOCYTIC MONONUCLEAR CELL IN PERIPHERAL BLOOD

FIRST REPORT OF STUDIES ON THE MONONUCLEAR CELLS OF THE BLOOD *

F. A. McJUNKIN, M.D.
MILWAUKEE

The purpose of this report is to describe a method by which a mononuclear cell constantly present in normal blood may be shown to be phagocytic, and to point out certain characters of the cell that suggest its origin.

The origin, morphology and many of the functional activities of the polymorphonuclear leukocytes (neutrophilic, eosinophilic and basophilic) of the blood are known, but considerable uncertainty exists in regard to the mononuclear group of leukocytes. While it seems quite certain that lymphoblastic cells constitute a large part of the mononuclear leukocytes, the classification of the remaining mononuclear cells that are present is not satisfactory. An important aid in tracing the origin of cells in sections of tissue is their relationship to the surrounding ones that divide to form them, but the leukocytes in the blood stream do not arise there by mitosis, and once they are swept away in the blood their position in regard to the other cells near them is no longer of value in tracing their origin. In face of the uncertainty concerning the mononuclear blood cells, terms such as transitional leukocyte, and large mononuclear leukocyte, that are not histologic terms imply a definite embryologic origin, have been commonly used.

Attempts at the identification and classification of nonlymphocytic mononuclear leukocytes have for the most part been based on staining characteristics. Methods dependent on the functional activities of the blood cells have, however, been employed, and of these vital staining has attracted most attention. The usual statement of observers employing this method is that cells which stain vitally do not appear in the peripheral blood, or they appear there in negligible numbers.

TECHNIC EMPLOYED

The method used is simple, but some of the details require considerable care in their execution. The object to be attained is to bring

* Submitted for publication Sept. 26, 1917.
* From the Pathological Laboratory of the Boston City Hospital.

the leukocytes into contact with fine particles of carbon at the body temperature and under exact and uniform conditions, and then to fix and stain them properly.

Three cubic centimeters of blood are added to 2 c.c. of 3.8 per cent. sterile sodium citrate that contains 1 per cent. by weight of a good commercial grade of lampblack. The citrate-lampblack liquid is shaken vigorously in the flask to secure as even a suspension as possible, and 2 c.c. immediately placed in a 15-c.c. graduated centrifuge tube to which the blood is added at once. To obtain the blood the palmar surface of a finger tip is painted with tincture of iodin, wiped with 95 per cent. alcohol, dried, punctured deeply with an automatic lance and the blood pressed out so that the drops fall directly into the tube. The citrated blood is mixed thoroughly by striking the lower end of the centrifuge tube with the finger and immediately is filtered through a single layer of muslin that has been laundered into a second centrifuge tube in order to remove the gross particles of lampblack. The second tube may be prepared by autoclaving it with the cloth pressed into its upper portion in the form of a cone. The cloth is moistened with a 3.8 per cent. citrate solution before the citrated blood is poured on it. It is not advisable to filter the suspension of lampblack before mixing with the blood because it tends to filter clear.

The filtered citrated blood is placed in a centrifuge and whirled at a moderate speed for fifteen minutes and at a high speed for five minutes. The tube is removed from the centrifuge and the black leukocytic layer on the surface of the corpuscles is carefully drawn with suction into a large bore hemocytometer pipet. Such a pipet may be kept in 80 per cent. alcohol and washed with sterile citrate before filling. The pipet is shaken for one minute, a wide rubber band stretched over it to close the ends, and then transferred to an incubator at 37.5 C. where it is kept in a horizontal position for one hour, being removed and shaken for one minute at the end of fifteen, thirty and forty-five minutes.

At the end of the hour the pipet is taken from the incubator, shaken for five minutes and coverglass preparations made in the usual way, the small drops of blood being placed on the coverglasses from the pipet. Slides are not suitable.

To stain the coverglass smear, 2 drops of a polychrome blood stain are placed on it for one minute. At the end of one minute four drops of distilled water are added and the diluted stain allowed to remain on it for two to three minutes. The stain is washed off with water, differentiated for ten seconds in 0.02 per cent. yellowish water-soluble eosin, washed with water, dried and mounted in colophonium-xylol.

Any polychrome blood stain that has a reaction properly adjusted may be used. The writer's blood stain obtained from Bausch and Lomb Optical Co., Rochester, N. Y., was employed in making most of the stains. If a number of preparations are to be stained the coverglasses are supported on the tops of small test tubes 12 mm. in diameter held in a test-tube rack, and the center of each pressed on with a 1-mm. glass rod while the alcoholic stain is spread out with a second rod. A single preparation may of course be held in suitable coverglass forceps.

The results and conclusions as recorded below are based on the preparations made by the foregoing technic. Since it would clearly be an advantage to employ a more direct method in the examination of pathologic blood, many variations of the test have been tried, but even slight variations have usually yielded negative results. It has not been possible to eliminate the centrifugation, but the undiluted blood

may be employed for making the smears, and this appears to be the simplest and most accurate way for the differential counting of leukocytes. In employing undiluted blood the ingestion of the carbon by the leukocytes is found to be determined by the concentration of the citrate. In the stained film there is no difficulty in distinguishing mononuclear cells containing carbon from polymorphonuclear ones that contain it, but the best picture is obtained if phagocytosis by the neutrophils is prevented. To do this 7.7 mg. of sodium citrate per c.c. of blood are used. This amount of citrate does not interfere with the phagocytic properties of the mononuclear cells, but 15 mg. prevent ingestion by all leukocytes. If only 5 mg. of citrate are used more than half of the neutrophils as well as the phagocytic mononuclear cells ingest the carbon.

To use the undiluted blood four small glass beads and 8 mg. of a dry lampblack-citrate powder are placed in a small test tube 45 mm. long prepared from glass tubing with an inside diameter of 7 mm., and 1 c.c. of water added. The tube is shaken and the upper surface of the liquid marked by scratching with a file. The liquid is washed out, the tube dried, the beads replaced, another 8 mg. of lampblack-citrate powder added and blood dropped into it from the finger until the upper surface reaches the mark. The finger is pricked with an automatic lance and the drops of blood allowed to touch the apex of a small wire in the shape of the inverted letter V inserted into the upper end of the tube. This prevents the blood from coming into contact with the mouth of the tube. The tube is stoppered with a rubber cork, vigorously shaken for five minutes, centrifuged at a moderate rate of speed for fifteen minutes and placed in the incubator for one-half hour at 37.5 C., care being taken not to disturb the leukocytic layer. The tube is removed from the incubator, shaken for two minutes, centrifuged, again incubated for one half hour, shaken for two minutes after removal from the incubator and coverglass preparations made and stained. The red and white hemocytometer pipet may be filled from the undiluted blood before the first incubation for the enumeration of the white cells and erythrocytes. The second shaking, centrifugation and incubation are required to bring all the leukocytes into contact with the carbon. The small drop of blood is placed on the coverglass by means of a capillary pipet with nipple attached. The films are allowed to dry in the air for at least three hours before the stain is applied.

The preparation of the lampblack-citrate powder is important. It is prepared by mixing intimately 7.7 gm. sodium citrate (Merck), U. S. P., of highest purity, that has been ground to small granules in a mill (not powdered in a mortar) with 0.3 gm. lampblack that has been ground in a mortar for thirty minutes. The powder is placed in a bottle and kept in a desiccator.

RESULTS OBTAINED

On examination of the smears with an oil-immersion lens the general picture is seen to resemble that obtained with any good polychrome stain. A striking difference, however, is observed in certain of the mononuclear cells the cytoplasm of which contains many carbon particles or is completely filled with the lampblack, while the lymphocytes and the great majority of the polymorphonuclear cells contain none, and those that do contain it have taken up a much smaller amount than

the phagocytic ones of the mononuclear group. The smears are surprisingly free from extracellular carbon deposited on the red blood corpuscles and in the plasma. Since not a single cell that is a lymphocyte of the small variety contains the particles, the phagocytic mononuclear cells as a result of the carbon they contain are readily distinguished. If it were not for the carbon within these cells, however, some of them would be mistaken for large lymphocytes, although most of them would fall in the classes commonly known as transitional and large mononuclear leukocytes.

The morphologic characters of the mononuclear phagocytic cell, aside from the ingested carbon, are well defined within certain limits, and most of the cells can be identified in the usual blood smear after the study of lampblack preparations; but all of them cannot be recognized with certainty. The average diameter of the cell closely approximates that of the polymorphonuclear neutrophil, but the individual cells present greater variations. Many are smaller than the neutrophils and approach the larger lymphocytes in size, while a few are larger than any neutrophil. The cell outline is usually round, but irregularities may be produced when the smear is made, or pseudopodia may be present as the result of ameboid activity.

The cytoplasm of this class of cells filled with the carbon particles is characteristic. Much lampblack is taken up by all cells of this variety, and many of them contain so great an amount that the character of the cytoplasm cannot be distinguished.

The zone of the cytoplasm is wide at some point, due to an indentation or eccentric position of the nucleus, and in preparations stained in the usual way this is, perhaps, next to its phagocytic properties, the most distinguishing feature of the cell. The cytoplasm is often present only in sufficient amount to form a distinct band about the nucleus, but it may be fully as wide as the nucleus itself. In those cells in which the cytoplasm is distinct it is seen to stain less blue than that of the lymphocytes. It may be quite free of granules, but usually there are present granules that are much like the neutrophilic granules, except that they are more filament-like. The filamentous granules color like those of the neutrophils by the oxydase reaction, but are usually less distinct. Typical discrete "azur" granules, such as occur so commonly in lymphocytes, have not been observed.

The nucleus is round or oval, is horseshoe or saddle-back in shape, or presents a broken irregular contour. Rarely a cell of this type is encountered in which the nucleus is stellate or divided into separate chromatin masses. Cells with this morphology appear to be formed during the hour of incubation, but it is not certain that an occasional cell of this class with a broken nucleus does not occur in the blood. The only important characteristic of the nucleus is that it is very rarely

both regular in outline and centrally placed. It stains less heavily than the nucleus of the neutrophils.

The number of this variety of cells in the blood of five normal individuals varies from 5.6 to 8.1 per cent., with an average of 7.2 per cent. In obtaining these percentages above 2,000 cells were counted in each sample and the direct method used, since it is not certain that the percentages in leukocytic layers after centrifugation are the same as in the whole blood. The average number of other cells is as follows: lymphocytes, 32.2 per cent.; neutrophils, 58.5 per cent.; eosinophils, 1.6 per cent.; basophils, 0.5 per cent. The average number of leukocytes present per c.mm. is 6,820. The coverglass preparations were mounted in pairs on slides and the cells counted from at least three such pairs with the use of a mechanical stage.

DISCUSSION AND CONCLUSIONS

The functional behavior of fixed tissue cells is constantly made use of in their identification, and of the cell functions phagocytosis is one that is important and has attracted a great deal of attention. In general the phagocytic properties of the cells commonly met with are known. Fibroblasts, identified by the use of appropriate stains, rarely or never are found to have incorporated foreign particles within their cytoplasm; none of the enormous number of lymphoblastic cells found in various normal and pathologic tissues are phagocytic; while polymorphonuclear neutrophils incorporate different bacteria and may ingest nonbacterial substances.

In the lesions of typhoid fever, in tubercles and in other pathologic processes endothelial cells divide, become free and migrate through the vessel wall into the extravascular tissue. This is seen in single oil-immersion fields of tissue that is perfectly preserved. These free mononuclear leukocytes of endothelial origin are frequently phagocytic for other tissue cells, red blood corpuscles, certain bacteria and for various nonbacterial particles such as carbon. The mononuclear cells of the blood shown by these experiments to be phagocytic for carbon correspond in morphology and phagocytic properties to the endothelial leukocytes of the tissues, and it seems likely that this class of leukocytes may prove to be of endothelial origin. That they are not related to the polymorphonuclear leukocytes is clearly shown by their phagocytic properties.

In order to determine the behavior of tissue cells during life, certain coal tar and natural dyes have been injected into animals intravenously and by other routes, and the tissues examined after a varying number of hours and days. Vitally stained cells are said not to be present in the peripheral blood of the animals treated in this way, but granules

of the stain are present in tissue cells spoken of as macrophages, which is a term implying that the cells containing the granules are capable of phagocytosis. The term phagocytosis is not correctly applied to the passage of a substance in solution into the protoplasm of a living cell, although it is there changed over into insoluble granules. It is not possible to say whether all phagocytic cells are vitally staining or not, but certainly intravital staining as commonly carried out is useless for the demonstration of phagocytic cells in the blood.

In designating the mononuclear cells of the blood that are phagocytic by the above method as a separate and distinct variety of leukocyte, factors other than the morphology of the cells are taken into account. Although the cells in the preceding experiments remain in the incubator for one hour only, they retain their ameboid activity and staining properties for four days at 37.5 C., and there is no reason to think that the behavior of the cells toward carbon particles under optimum conditions in vitro is in any way an abnormal manifestation. That all cells have an opportunity to ingest by phagocytosis the carbon and yet that none but this variety do ingest it is shown by the presence of the large amount ingested and its absence from other cells except a few of the polymorphonuclear neutrophils.

Since none of the small mononuclear cells that are typical lymphocytes ingest the carbon, it is evident that lymphocytes and phagocytic mononuclear cells are comprised in the mononuclear group of leukocytes. It is believed that all of the phagocytic cells, owing to their resemblance to large lymphocytes especially, cannot be accurately identified by means of any of the blood stains now in common use without the employment of a reaction to determine their phagocytic properties.

[The writer gratefully acknowledges his obligation to Dr. F. B. Mallory for the privilege of carrying on this work in his laboratory and his indebtedness to Mr. L. Massopust for the illustration which accompanies this paper.]

Description of Plate

Drawn with camera lucida and oil-immersion lens from a single cover-glass preparation.

A, group consisting of neutrophil, erythrocyte and mononuclear cell containing carbon; outline of nucleus of phagocytic cell is a broken curve.

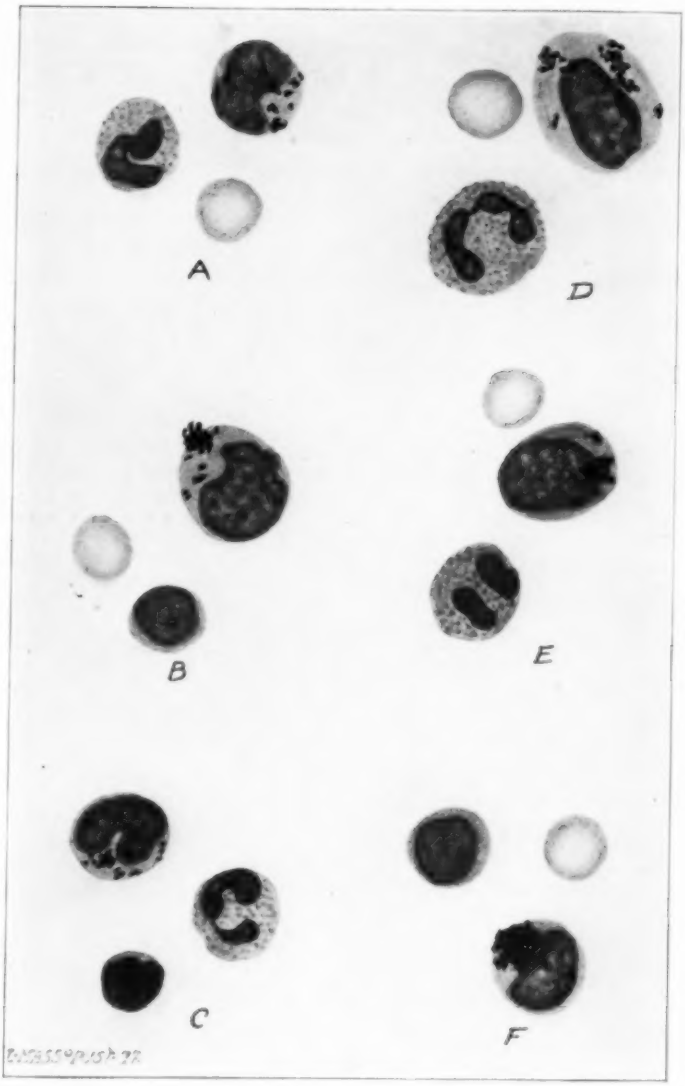
B, lymphocyte, erythrocyte and phagocytic cell with an irregular nucleus.

C, lymphocyte, neutrophil and phagocytic cell with saddleback nucleus.

D, neutrophil, erythrocyte and phagocytic cell. Note that all elements in this part of the coverglass smear are large. The nucleus of the carbon-containing cell is oval.

E, erythrocyte, neutrophil and phagocytic cell with oval nucleus.

F, erythrocyte, lymphocyte and phagocytic mononuclear. The phagocytic cell resembles the lymphocyte morphologically.


A
D
B
E
C
F

CALCIFICATION IN THE PINEAL GLAND*

ERNST P. BOAS, M.D., AND THOMAS SCHOLZ, M.D.
NEW YORK

Pathologic as well as roentgenologic literature on calcification of the pineal gland is very scarce. Schueller,[1] apparently, was the first to demonstrate concretions in the gland radiographically, and the only one to verify his roentgen-ray findings by necropsy. The roentgenograph of the skull (lateral view) in patients with pineal calcification shows characteristically a more or less dense shadow, varying in size from a pinpoint to a split pea, and situated from 4 to 5 cm. behind and slightly above the level of the tip of the posterior clinoid process.

We have recently seen a case in which the roentgen plate of the skull showed such a shadow and in which the necropsy revealed a definite calcification of the pineal gland.

Our patient was 74 years of age. The cause of death was a strangulated, sliding hernia of the sigmoid. The pineal shadow was an accidental finding, no symptoms having pointed to disease of the gland. About two years before his death the patient suddenly became unconscious and for two months after that remained in bed stuporous, unable to speak, with involuntary urination and defecation. He apparently recovered completely from this attack and on admission to the hospital presented no neurologic symptoms whatever. On necropsy areas of softening were found in his brain involving the external capsule, the putamen, and the island of Reil on the right side. In addition, he had primary contracted kidneys, cholelithiasis, and an extreme arteriosclerosis and calcification of the coronary arteries, with calcification of a large part of the myocardium of the left ventricle.

Roentgenologic examination of the skull with the patient in a lateral position presented a dense, somewhat irregularly outlined shadow of about the size of a split pea, 4 or 5 cm. posterior to and somewhat above the tip of the posterior clinoid process. In both lateral views the shadow appeared of exactly the same size. The cranial bones failed to show any abnormality.

The following is an extract from the necropsy protocol:

The pineal body is slightly enlarged. It is calcified in large part. The calcium is deposited as a loose, spongy framework, chiefly in the upper half of the gland. A few small calcified plaques 1 or 2 mm. in diameter project from the posterior surface of the pineal gland into the third ventricle. There is no acervulus in the choroidal plexus or in the ependyma covering the trigonum habenulae.

Many sections were taken for microscopic examination. In the lower half of the gland the normal cellular structure persists. The nuclei are well preserved, large and vesicular, with a moderate amount of chromatin. There is

* Submitted for publication Sept. 20, 1917.

* From the Pathological and Roentgenological Departments of the Montefiore Home and Hospital.

1. Schueller, A.: Verhandlungen des Vereins für Psychiatrie und Neurologie in Wien. Wiener klin. Wchnschr., 1909, **22,** 1143; *ibid.*, Roentgendiagnostik der Erkrankungen des Schädels und Gehirns. Centralbl. f. d. Grenzgeb. d. Med. u. Chir., 1909, **12,** 849.

apparently some increase in the fibrous stroma of the gland. Scattered here and there are many small grains of typical brain sand (acervulus cerebri) They stain blue with hematoxylin and are laid down in concentric lamellae. They are approximately circular in shape but their margin is irregular. There is no tissue reaction about them, but they lie apparently free in between the glandular tissue. The upper portion of the gland is largely replaced by an irregular, blue-staining mass. On close inspection it is apparent that this mass has been formed by the fusion of innumerable small grains of acervulus. Under the high power the concentric rings of each grain can still be distinguished. The tissue between the adjacent granules stains less deeply with hematoxylin, and appears to be less deeply infiltrated with calcium. About the periphery of this mass of fused granules of brain sand there are many discrete granules

Fig. 1.—Skull plate showing shadow 4.5 cm. posterior to the posterior clinoid process.

similar to those first described. However, many of them have become agminated into small, mulberry-shaped masses. In one small area in the lower portion of the gland, rather wide, anastomosing trabeculae of delicate, fibrous tissue enclosing many small capillaries divide the grandular tissue into imperfect alveoli. The blood vessels are normal. The blood vessels of the choroidal plexus are normal. Its epithelium is low cuboidal in type, with well staining nuclei. A few small granules of acervulus are present.

Acervulus cerebri or brain sand is found very frequently in the pineal gland, in the choroidal plexus and in the neuroglia covering the commissura habenulae. It is present as early as the seventh year of

Fig. 2.—Roentgenogram of necropsy specimen of brain in same position as skull plate in Figure 1.

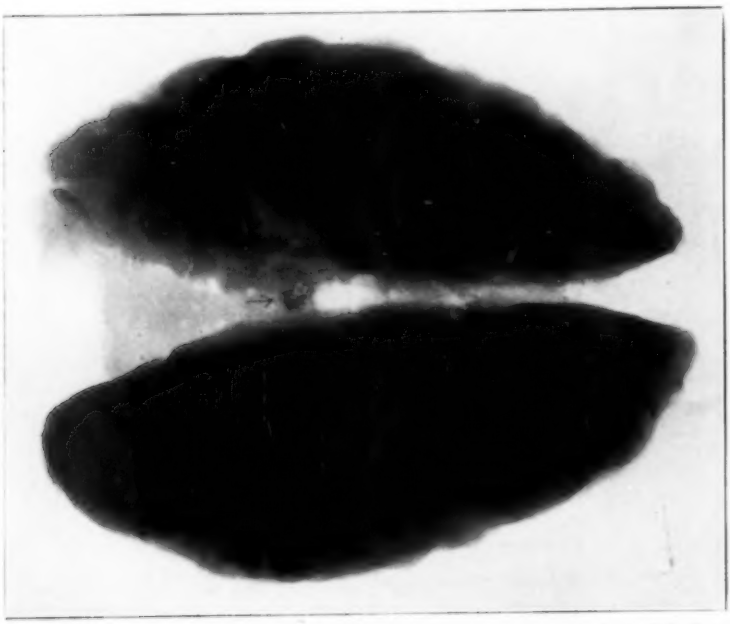


Fig. 3.—Roentgenogram of necropsy specimen of brain, craniocaudal view. A number of other small shadows are due to calcification of the meninges.

life and increases in amount with age. The concretions are sometimes mulberry-shaped, and are composed of calcium phosphate and carbonate. Krabbe,[2] in his study of over a hundred pineal glands, saw these concretions very often. In studying serial sections he found that they are completely surrounded by parenchyma without being in contact with the connective tissue. In a few cases he observed calcifications in the connective tissue septa. These were very small and of an oblong shape. Marburg[3] believes that brain sand is the first sign of involution of the pineal gland. The earliest deposition is in the commissura habenulae. An increase in the size and number of the connective tissue septa, with calcification, may occur. Through apposition and fusion the corpora arenacea may assume many shapes. The size of the concretions varies from the size of a leukocyte to one third of the size of the gland. As far as Marburg could determine, age is the only factor predisposing to the calcification of the pineal gland. In Schueller's case, in which the pineal calcification was demonstrated radiographically, and in which Erdheim verified the interpretation on necropsy, no detailed description of the pathologic findings is given except that calcified deposits were also found in the posterior commissure. In our case, in addition to the individual small concretions and the small mulberry-shaped masses, there is the fusion of a great number of concretions into large irregular masses. This is well shown in the photomicrographs.

Roentgenologic demonstration of the pineal calcification has become more frequent in recent years, due to improvement in technic, and especially due to the increased interest in neurologic roentgen-ray work. A more careful technic adopted lately in our roentgen-ray department with the view, possibly, to visualize even minute pineal shadows, which so easily are overlooked in routine examinations of the skull, proved of value. Up to the present we have had ten cases showing more or less distinct pineal shadows on the roentgen plate. All of them were neurologically normal adults, with the exception of one, a man of 45 years, in which the diagnosis was muscular dystrophy.

Various authors have described certain definite syndromes as due to disease of the pineal, but only two of them report in connection with those syndromes a roentgen-ray shadow in the pineal region, and only one of them emphasizes this roentgenographic finding: Horrax[4] mentions a case of a girl with precocious sexual development at 11 years,

2. Krabbe, K.: Sur la glande pinéale chez l'homme, Nouv. Iconog. de la Salpêtrière, 1911, p. 257.

3. Marburg, O.: Zur Kenntniss der normalen and pathologischen Histologie der Zirbeldrüse, Arb. a. d. Neurolog. Institut. Wien., 1909, p. 217.

4. Horrax, G.: Studies on the Pineal Gland, THE ARCHIVES INT. MED., May, 1916, **17,** 607.

Fig. 4.—Cross section of brain through middle of pineal body.

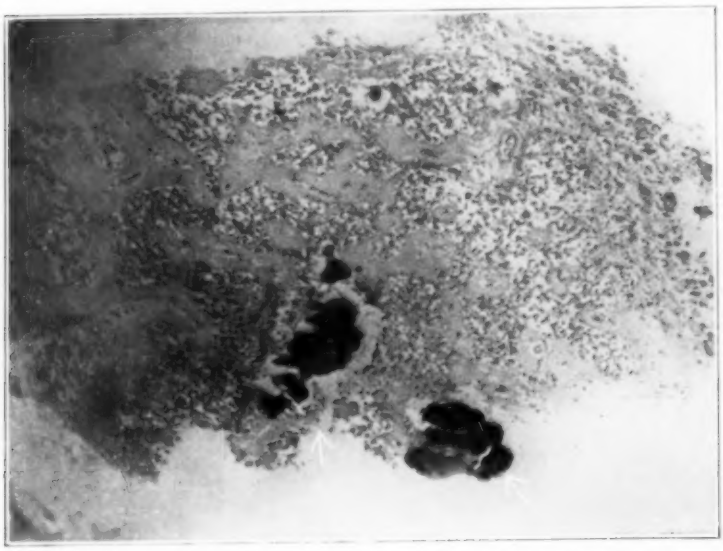


Fig. 5.—Low power photomicrograph showing islands of calcification in pineal gland.

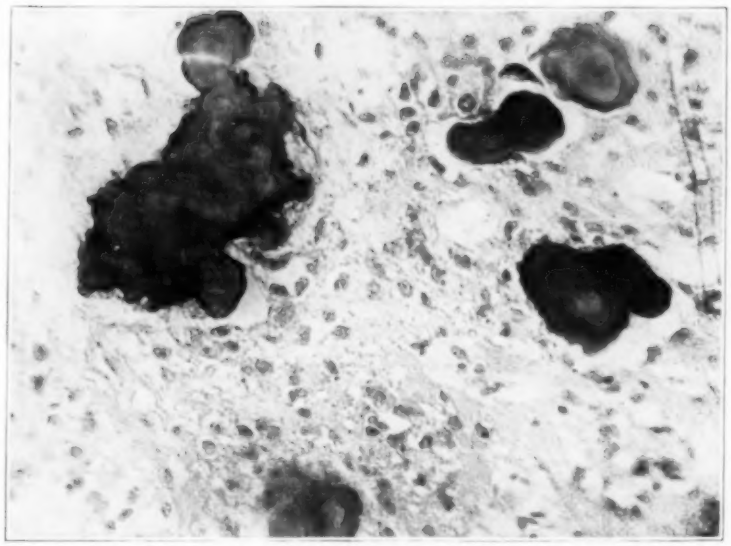


Fig. 6.—Medium magnification showing characteristic cells of pineal gland and islands of calcification.

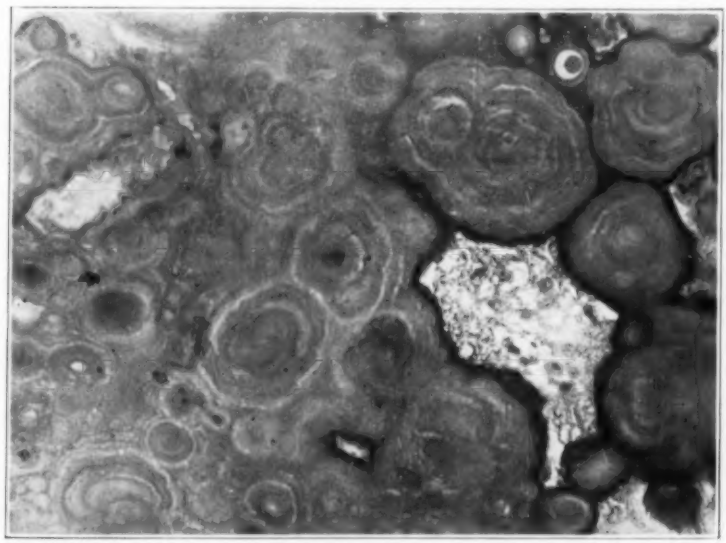


Fig. 7.—High power showing minute details of calcified area; concentrically arranged lamellae.

in whom a pineal shadow was demonstrated by roentgen-ray examination. Timme[5] recently published a series of cases of progressive muscular dystrophy. Five of these patients were examined roentgenologically and four of them, who were above the age of puberty, showed shadows in the pineal region. The youngest patient, 14 years of age, failed to show any shadow. As the patients were quite young and symptoms of their disease had begun in childhood, it is possible that in these cases the pineal gland was diseased and so lent itself more readily to the process of calcification; or more probably, involution of the gland may have occurred earlier than normal, with consequent exaggeration of the deposit of brain sand.

In our case the calcification of the pineal is an evidence of the degenerative processes of senescence, which are manifested as well by the extreme arteriosclerosis and calcification elsewhere in the body. It is not astonishing that there were no symptoms referable to the pineal gland. Whatever function the pineal gland may have is exercised before puberty. The pineal secretion is supposed to inhibit growth. With pineal disease this inhibition is removed and there is adiposity, general bodily overgrowth, with precocious sexual development, increase in size and development of the sex organs, and precocious change of voice in boys. After puberty the pineal gland undergoes involution, and so one would not expect symptoms from pineal calcification after adolescence.

CONCLUSIONS

Shadows due to calcification in the pineal gland are found quite frequently in roentgenograms of the skull. In the vast majority of cases the calcification is only an exaggeration of the deposit of brain sand found normally in the pineal gland of adults. As would be expected, these shadows are found more frequently with advancing age. Since the calcification occurs in the course of the normal involution of the pineal gland, it has no significance except in very young individuals. In these it may be an evidence of an abnormally early involution of the pineal gland, which, if it occurs at the period when the gland is normally physiologically active, may cause symptoms due to insufficiency of the pineal secretion.

5. Timme, W.: Progressive Muscular Dystrophy as an Endocrine Disease, THE ARCHIVES INT. MED., 1917, **19,** 79.

ANATOMIC OBSERVATIONS CONCERNING THE MECHANISM OF BILE RESORPTION IN JAUNDICE *

HORST OERTEL, M.D.
MONTREAL, QUE.

The manner in which bile is resorbed from the liver into the blood, general circulation and tissues presents much that is still unclear and uncertain.

The subject is complicated by our imperfect knowledge of the finer structure of the liver. For, while the direct relation of the liver cells to blood and bile capillaries is not quite definitely settled, there exists no agreement whatever as to the presence or absence of lymph channels in the acini. It is held by some that perivascular lymph sheaths lie between liver cells and capillaries,[1] while others positively deny this.[2]

The question, then, as to whether bile resorption in the liver occurs as the result of primary lymph or direct blood resorption, is complicated by anatomic uncertainty.

The physiologic experiment is unable to solve this problem, for not only are the observations and conclusions of experimenters quite contradictory,[3] but lymph and blood have naturally been collected for analysis outside of the liver, sometimes at considerable distance, where a relation to the primary channels of resorption cannot with certainty be determined, and in which modifications by collateral circulation, secondary diffusion and other possible influences on bile contents of lymph and blood, cannot be satisfactorily estimated.

---

* Submitted for publication July 21, 1917.

* From the pathological laboratories of the Royal Victoria Hospital and of McGill University.

1. Disse: Arch. f. mikr. Anat., 1890, **36.** Bürker: Pflüger's Arch. f. Ges. Physiol., 1901, **83,** 241. Eppinger, Jr.: Ziegler's Beitr. z. path. Anat. u. z. allg. Path., 1902, **31,** 230. Kretz: Ergebn. d. allg. Path. u. path. Anat., 1904, **2,** 502. Ibid., Handb. d. allg. Path., v. Marchand and Krehl, 1913, **2,** Part 2, p. 468. Reinke: Verhandl. d. anat. Gesellsch., 1898, No. 12.

2. Schäfer: Textbook of Microscopic Anatomy. Longmans, Green Co., 1912, p. 571. Herring and Simpson: Proc. Roy. Soc. Med. and Surg., 1906, **78.** Browicz: Bull. Acad. d. Sc. de Cracovie, July, 1899, January and May, 1900. Teichmann: Abhandl. d. k. preuss. Akad. d. Wissensch. Krakau. 1899, **34.** Kaufmann: Spec. Path. Anat., Berlin, Georg Reimer, 1911, **1,** 565.

3. Kaufmann: Spec. Path. Anat., Berlin, Georg Reimer, 1911, **1,** 637. Kretz: Ergebn. d. Path. u. path. Anat., 1904, **2,** 502; Ibid., Handb. d. allg. Path., v. Marchand and Krehl, 1913, **2,** Part 2, p. 468. Whipple and King: Jour. Exper. Med., 1911, **13,** 115.

If the immediate path of bile resorption remains undecided, it is generally conceded that the mediate cause lies in bile obstruction in, or outside of, the liver by either coarse mechanical means or finer intrahepatic impediments to the bile flow: cholangeitis, pericholangeitis, bile thrombi or a thick, so-called pleiomorphous bile.

I.

The conditions consequent on the first cause, that is, coarse mechanical occlusion of the larger bile ducts, are perhaps best understood and commonly summarized under the term obstructive jaundice. The classic example of obstructive jaundice is stone in the common duct, which may either obliterate the duct entirely, or, at least, narrow it to such an extent as to bring about dilatation and backward pressure into all other bile ducts, which gradually extend into the bile capillaries. Bile consequently stagnates, ultimately bile capillaries rupture, and finally bile imbibition with necrosis of the liver cells results.

This well known, common picture may be variously modified and complicated by accompanying infections and inflammatory changes. Very similar, of course, are the results from obliterations or partial obstructions of the hepatic duct.

During the later stages of obstructive icterus certain changes occur in the contents of the larger bile vessels, the most conspicuous of which is gradual resorption of bile pigment and substitution of the bile by a thick or thin mucoid, viscid fluid, so that the bile canals appear finally as cystic dilatations.

As simple and easy of comprehension as this course of events seems on first sight, and as it has been fixed in our mind by experience, there still remain some links in this chain which need strengthening, especially in the light of some unusual but very notable and positive exceptions to the rule.

A particularly impressive exception which, in a way, carries the weight of an experiment, came recently to necropsy in these laboratories. It illustrates, quite apart from its theoretical importance, that a considerable, if not complete, obstruction of the common bile duct and hepatic ducts may occur, sufficient to produce ecstasy even in their smaller branches in the liver, without any general or even local hepatic jaundice and, apparently, even without subjective symptoms.

As far as can be determined, the case differs in extent and manner of obstruction from those mentioned in literature unfortunately only in a casual way without the care which they deserve.

Thus, Rolleston[4] says:

4. Rolleston: Diseases of the Liver. Macmillan, 1912, p. 749. Griffon: Bull. Soc. anat., Paris, 1896, **71**, 513. (Quoted by Rolleston.)

Jaundice which has been marked early in the course of impaction, may wane and finally disappear, and after death a loose calculus may be found in the duct. Griffon records four cases of this kind in which the calculus was found just above the biliary papilla. . . . In exceptional instances there may never at any time be jaundice, although the common duct contains calculi.

Unfortunately, no mention is made of the size of these calculi, their exact position, physical constitution and stability or mobility, and whether they lead in the cases referred to, to obstruction, back pressure and dilatation of the ducts. This is, of course, the all important matter in the production of jaundice.

Kaufmann[5] also refers to such instances in a cursory way. He writes, in reference to obstructions of the common duct: "In rare cases a tremendous stone may occur (as author saw, over thumbthick) without jaundice." But he gives no further details. Aschoff[6] makes no mention of such cases. Ziegler[7] also makes no reference to these exceptions.

REPORT OF CASE

History.—The case observed in these laboratories concerns a man 73 years of age who was admitted to the Royal Victoria Hospital July 12, 1916, and who died July 17, 1916.

He complained of inability to pass urine, and of constipation for the previous three months. For two weeks before admission catheterization had been employed. He had lost considerable weight, was rather poorly nourished, but showed no other abnormal physical signs and gave no history of other symptoms.

Family history and personal history were negative, and he gave no account of any previous illness.

Examination.—Examination disclosed a smooth, but irregular, hypertrophied prostate. The urine contained some blood and pus cells.

Operation.—July 13, under local anesthesia, the first stage of a prostatectomy by suprapubic incision, with drainage, was performed.

July 15 the patient's general condition was much worse; pulse became weak and irregular and he died July 17, at 9:30 p. m.

Necropsy.—Necropsy (117'16) showed the body of a man of about the age stated, 175 cm. in length, of good frame, but of poor nutrition; skin pale and clear, with a number of ecchymotic spots on the right shoulder and axilla; pupils were unequal, conjunctivae clear.

Section disclosed no free fluid in the abdominal cavity; several loops of small intestine in the lower left quadrant were dark greenish in color and there were numerous recent fibrinous adhesions between different loops of bowel and parietal peritoneum in the region of the descending colon. Outside of an enlarged prostate, no other essential lesions were found except the following unsuspected condition of the liver and bile ducts: While still in situ a very marked dilatation of the extrahepatic bile ducts was noticeable. The gallbladder, on palpation, revealed a large number of stones, but some thin bile could be squeezed with difficulty from the gallbladder into the duodenum.

On palpation of the thick common duct a large calculus was found, located, practically impacted, at the ampulla of Vater (Fig. 1). On opening the common duct this gallstone was oblong, egg-shaped, and measured 3 by 1.5 cm.

5. Kaufmann: Spec. Path. Anat., Berlin, Georg Reimer, 1911, **1**, 631.
6. Aschoff: Path. Anat., II, Jena, Gustav Fisher, 1913, p. 914.
7. Ziegler: Spec. path. Anat., Jena, Gustav Fischer, 1902, p. 651.

The duct itself measured at the papilla 3 cm. in diameter. Following the duct upward, it was found to contain three other large, irregular, cherrystone-sized, as well as a number of smaller, pea-sized stones, six in number. It was markedly dilated throughout; its widest portion, about 5.5 cm. above the papilla, measured 4 cm. in diameter. At the junction of the cystic and hepatic ducts the diameter was also 4 cm.

The much dilated main hepatic duct contained one large, firmly lodged calculus rather irregularly triangular in shape and the size of a large cherrystone. Above it were seven smaller, pea-sized, loose stones varying somewhat in size. This duct measured 2.25 cm. in diameter.

The right branch of the main hepatic duct contained four large pea-sized stones and a number of other seedlike concretions. It measured 1 cm. in diameter.

The left branch of the main hepatic duct contained a large pea-sized stone and also a number of seedlike concretions. Its diameter was 1.5 cm.

The intralobar ducts were visibly dilated and measured from 2 to 4 cm. in diameter. Many contained fine granular bile precipitations. Smaller, pointlike, greenish discolored ducts were also to be seen in the liver substance; the parenchyma, however, was not jaundiced, but rather pale, reddish brown, with indistinct markings, and generally intact and firm.

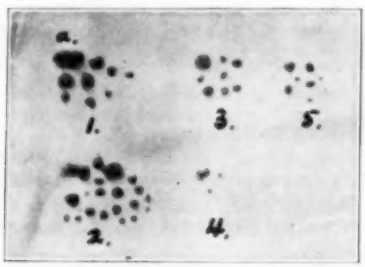


Fig. 1.—Photograph of gallstones found in case of obstruction of bile ducts without icterus. 1. Stones contained in common duct; *a*. Large stone impacted at ampulla. 2. Stones in gallbladder. 3. Stones in main hepatic duct. 4. Stones in hepatic duct of left lobe in liver. 5. Stones in hepatic duct of right lobe in liver. (For further description see text.)

The dilated bile ducts did not show any thickening of their walls, but were stained a bright green. But this discoloration extended nowhere into the surrounding liver substance.

The cystic duct measured 0.5 cm. at its origin.

The gallbladder was distended, contained some yellowish bile and a large number, about twenty, of variously sized and irregularly shaped stones.

The consistency of all stones was very firm, hard, with rounded, smooth but strong edges.

Analysis showed the calculi to be largely cholesterin precipitated around an organic nucleus, with a considerable amount of bile pigment.

Microscopic Examination.—Microscopic examination of the liver showed parenchyma and interlobular tissue intact. There was nowhere dilatation, bile engorgement or inflammation of the interlobular bile ducts, and the columnar arrangement of the liver cells within the acini was not disturbed. The acinar blood capillaries were somewhat engorged, especially around central veins, but bile precipitation or engorgement of bile capillaries was entirely lacking and liver cells appeared uniformly healthy.

We are dealing, therefore, in this instance with an apparently marked obstruction of the large intrahepatic and extrahepatic bile ducts, which, however, has not extended into the smaller interlobular ducts and acinar bile capillaries.

The question arises how to explain this, more especially, how to account for absence of bile stasis in the parenchyma and lack of icterus.

There can be no question that the obstruction was severe, if not complete. All anatomic evidence points in that direction: the location, size, consistency and number of stones as well as the tremendous, sausage-like dilatation of the ducts themselves. Whether the obstruction was ever an absolute one is of course not possible to answer with certainty, for we possess no record of the color of feces during life, and the necropsy protocol does not specify any abnormality in them. However, this is not, it seems to me, of essential importance, for admitting some bile to have escaped, which is indeed quite possible, it is certain that the obstruction was sufficient to cause ecstasy of the bile ducts. It remains, then, to be answered why this did not extend to and include the interlobular ducts and intra-acinar bile capillaries and liver cells. Every pathologic anatomist will recall cases of severe obstructive jaundice in which the obstruction appeared less complete and the dilatation of the ducts less pronounced than here, and still was considered sufficient to account for the occurrence of icterus. It follows, therefore, that additional factors enter into its formation besides the mere mechanical blocking of the ducts. One of these is well known, and I shall simply mention it in passing, for it does not directly concern this issue, namely, inflammation of the bile ducts. An even moderate stasis may, by secondary ascending cholangeitis and pericholangeitis, lead to severe jaundice. But such cases are not of pure stasis, unlike the case here before us, and they stand, therefore, outside of this discussion.

One other point must be settled at the start, namely, whether this case belongs to the rare category, mentioned by Rolleston, in which fading of pigmentation, almost to disappearance, occurs. Judging from the meager records, this appears to follow a reestablishment of bile flow in which, therefore, the obstruction, say from one stone, was relieved by mobilizing it. That is not comparable to this case at all. Moreover, the entire integrity of the liver cells, the general preservation of their architecture, the lack of necroses or evidences of regeneration as seen after necroses, together with the perfectly normal appearance and arrangement of interlobular structures, make a previous jaundice most improbable; for such a complete, uniform recovery from what must have been a severe and lasting icterus to absolutely normal conditions in a case in which, as we know, the obstruction has not been relieved, seems to me impossible. The explanation must, therefore, be sought elsewhere.

Now it is well known that a resorption of bile in the liver occurs only with the existence of considerable over-pressure. Bürker has shown that this follows an overpressure of 20 mm. Hg. The place of resorption is in the portal zone of the liver parenchyma, not from the interlobular ducts lined by cylindrical epithelium. It is evident, therefore, that the pressure in the parenchyma can never have risen here sufficiently to force the bile back into, or interfere with the discharge of bile from, the bile canaliculi and interlobular ducts. This much seems certain, but just how and why this was avoided can, with our present knowledge, only be surmised.

In the first place, much may depend on the manner and rapidity with which obstruction occurs. When an obstruction takes place slowly and gradually (not unlikely in this case by entire absence of subjective history or symptoms) the results are apt to be very different from rapid occlusion with normal bile flow. For it is conceivable that when the bile stagnation in the larger ducts has gradually reached a certain degree, diminution or even cessation of bile formation may occur. (Reflex action?) The pressure of the bile may, therefore, never become great enough, especially if some slight outflow is intermittently possible, to extend to the interlobular bile ducts and to the acinar canaliculi, although a sufficient bile volume may gradually accumulate in the larger and extrahepatic ducts to cause them to dilate.[8]

The character of the bile itself must also be of importance. For a thin, watery bile would not only be less apt to exert overpressure, but would, by virtue of its easy flow, be more apt to escape by the obstructing agent into the duodenum and thus just counterbalance a rise of pressure through the interlobular ducts into the bile capillaries. A thick, slowly flowing, viscid bile would naturally have opposite effects.

I consider, therefore, that rapidity and manner of obstruction, together with the character of the bile, are most probably of fundamental importance in the results of interference with the bile flow through the large extrahepatic ducts; thus, even severe obstruction may be regulated by a gradual adaptation to the new conditions and the creation, so to speak, of a new mechanism of bile elimination.

I might in this connection refer here briefly to another case, recently under observation, of a woman, 48 years of age, dead from hemorrhage after hysterectomy and cholecystotomy for gallstones. Necropsy (50 '17) disclosed two small, loose stones in the hepatic duct 2 cm. above the junction with the common duct. Above this point the larger branches of the hepatic duct showed moderate dilatation. There was no general jaundice. The liver weighed 1,600 gm., was pale mottled,

8. Experiments with regard to these points are at present conducted in our laboratories.

yellowish and very friable, fatty, with indistinct markings. Microscopically, the liver showed patchy, irregular bile precipitation in limited areas around the central veins in swollen, fatty, vacuolated liver cells with much blood stasis, but no general icterus, no diffuse bile imbibition of liver cells or bile in the acinar canaliculi. The lobular periphery, particularly, was everywhere free from bile. Evidently this patchy, limited, central bile retention in liver cells was in this instance not due to extrahepatic obstruction at all, and was probably attributable to other causes: namely, severe venous congestion with subsequent changes in the liver cells.

It would be instructive to obtain in similar rare or unusual cases detailed information and analysis regarding the points here discussed and thus gain a more exact knowledge of the conditions underlying icterus consequent on pure obstruction of common or hepatic duct than we command at present.

II

If we have seen that the conditions leading to jaundice in pure obstruction are not as simple as they appear at first sight, they become much more complicated in those cases in which no gross obstruction may be discovered; that is, in the various forms of so-called hematogenous, toxemic or hematic icterus. That the liver is essential for its production is now generally conceded, although the observations of Whipple and Hooper[9] seem to indicate that bile may be formed on intravenous injection of hemoglobin into dogs after exclusion of the liver from the circulation, and the investigations of Joannavics[10] point to the necessity of the spleen as a preparator of blood corpuscles for the production of bile by the liver. Its exact mechanism is, however, not definitely known. Most generally accepted are the ideas of Stadelmann,[11] Minkowski,[12] and the more definite views of Eppinger, Jr., according to which an excessive production of a pleiochromous, thick bile occurs (hypercholia) which cannot be normally discharged, and therefore enters the blood (parapedesis). Eppinger, Jr.,[13] has furnished a more definite anatomic conception by demonstrating bile thrombi (intracapillary bile thrombosis) in the liver of these cases. According to these views, the hematogenous jaundice is, in the last instance, an intra-acinar obstructive jaundice.

---

9. Whipple and Hooper: Jour. Exper. Med., 1913, **17,** 593 and 612.

10. Joannavics: Ztschr. f. Heilk., Path. Abt., 1904, **25,** 25; Ibid., Recherches experimentales sur la pathogenese de l'icters. Prize essay. Brusseles, 1903.

11. Stadelmann: Der Icterus, Stuttgart, 1891.

12. Minkowski: Kongress f. inn. Med., 1894; Ibid., Ergehn. d. Path. u. path. Anat., 1897, **2.**

13. Eppinger, Jr.: Ziegler's Beitr. z. path. Anat. u. z. allg. Path., 1902, **31,** 230, and 1903, **33,** 123.

It is particularly in this connection that the question of bile absorption by lymph or blood stream has been actively discussed. Eppinger, Jr., Kretz and others firmly believe in the existence of intra-acinar lymph channels, while again others (notably anatomists and histologists) deny their existence entirely. The views of Eppinger, Jr., and Kretz are largely based on pathologic evidence. In edematous livers and those in which loss or shrinkage of liver cells occurs, there appear definite perivascular sheaths between capillaries and liver cells, occasionally filled with amorphous coagulum. These are regarded by them as perivascular lymph spaces or roots of lymphatics. I have convinced myself of their existence in a number of livers.

The stain which I have long employed for these and other sections in which exact definition, differentiation and contrast are desired consists in deeply staining paraffin sections in hematoxylin (long washing with few drops of concentrated solution of lithium carbonate added to the wash water), immersion in a concentrated solution of picric acid, with almost immediate withdrawal and thorough washing in abundance of water.

Counterstain with a solution of watery eosin, prepared by adding drop by drop a strong solution of eosin to a large test tube of water until the color of the water is bright red, for about thirty to forty-five seconds. Wash thoroughly in water, rapidly dehydrate, clear in oil of bergamot, mount. (It is well to control each step under low power of the microscope.) Protoplasm stains purplish, nuclei deep blue, red cells yellow, fibrous tissue pink. Cell and nuclear outlines and definitions, reticulum, and contrasts come out exceedingly well by this method. It is more delicate than Van Gieson's stain, and well adapted for microphotographic purposes. In suitable cases the perivascular spaces are definite and plain according to this method. But I am conscious that it is difficult to exclude artefacts; that is, an artificial separation of capillaries from the cells. Nevertheless, it must be admitted that their general and uniform appearance in cerain cases argues against that view, as well as observations in jaundiced livers to which I shall refer later.

To return to the consideration of the mechanism by which toxic or hematic icterus is produced: The observations and views of Minkowski,[12] Stadelmann[11] and Eppinger, Jr.,[13] which are strongly supported by Kretz, furnish a satisfactory explanation for a number of these cases, but by no means for all. For there are others in which neither a thick, pleomorphous bile nor bile thrombi can be demonstrated. Every pathologic anatomist recalls cases of hematogenous icterus in which these are absent. It is, therefore, necessary to account for them in some other way.

It has been suggested that bile thrombi, the original cause of the icterus, have disappeared;[11] this is a view I cannot share, for the whole histologic picture in many of these cases is quite different from those due to pleomorphous bile and bile thrombi. Instead of coarse, plump precipitations and coagulations in intercellular canaliculi and liver cells, these cases show a fine, diffuse, granular bile precipitation in the protoplasm of the liver cells, usually with cell swelling and patchy cell

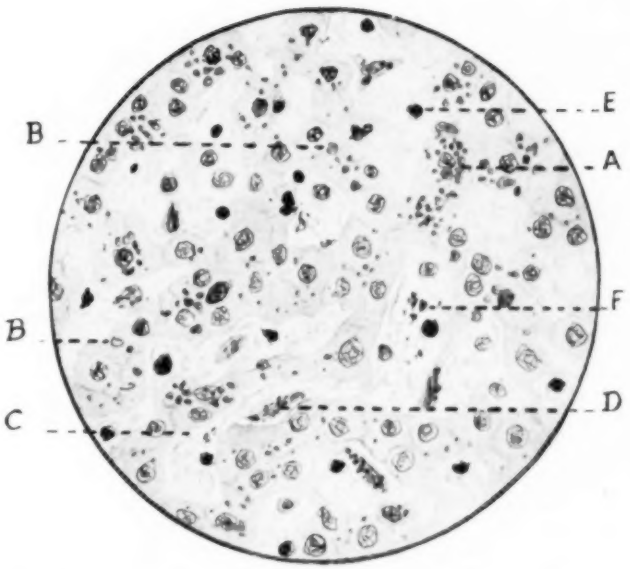


Fig. 2.—Microscopic section from liver in hematogenous icterus in pernicious vomiting of pregnancy. (Zeiss Object. 4 mm. D. D. Ocular 8.) *a*. Liver cells containing diffuse granular and clumpy bile pigment, partly in process of solution. *b*. Fading and bile forming red blood cells within liver cells. *c*. Perivascular space with bile pigment passing into capillary. *d*. Lining endothelial cell of capillary containing bile pigment. *e*. Leukocyte with bile pigment. *f*. Capillary lumen with free granular bile pigment. (Hematoxylin-picric acid-eosin stain.)

loss. It has been suggested by Sterling[14] that jaundice may result from injury to liver cells, which leads to disorganizations or occlusion of the smallest intracellular bile canals by swelling or fibrin plugs. But the great objection to this explanation is the fact that relatively few cases of parenchymatous degeneration or edema in the liver are associated with bile retention and resorption, and that even quite general and extensive necroses may occur without the slightest evidence of jaundice or even local bile precipitation. I have only recently examined the liver from a patient with fatal septicemia consequent to gangrene of the gut in a strangulated hernia, which showed very prettily all stages of pure toxic liver necroses; but there was nowhere any evidence of icterus.

The same is true of chronic venous congestion in which, as I[15] have pointed out elsewhere, severe jaundice may occur, particularly toward the end of the process. On the other hand, jaundice may be absent even in quite extensive necroses in venous cyanosis, or at least may lead only to slight icteric tinge of conjunctivae with very little evidence of bile precipitation and resorption in the liver itself. Plainly, therefore, parenchymatous swelling, cell loss, even extensive necroses are in themselves not sufficient to account for jaundice. Something else is also essential.

Some light may be thrown on this question by observations I have recently made in a number of cases of hematogenous jaundice to which the views of Stadelmann and Eppinger, Jr., seemed not applicable. They were cases of sepsis, pneumonia, and toxic lesions of pregnancy accompanied by definite general icterus. It has already been said that these cases presented a characteristic histologic picture. Bile was rather diffusely "dusted" or "sprinkled," mostly in fine granules, spherules and minute clumps throughout the liver sections. Closer inspection showed it precipitated within turbid protoplasm of degenerating and fading liver cells. These precipitations did not correspond to intracellular casts of fine canaliculi. On the contrary, none of these could be discovered. Higher magnification showed further characteristic pictures, which were especially well displayed in the liver of a woman dead with marked jaundice from toxic vomiting in pregnancy (Fig. 2.) (Necropsy 25, '17.) Here it was seen that the fine, granular pigment was gradually set free from the liver cells, possibly washed away, but frequently by direct fading and loss of cells. It was then to be observed in the perivascular sheaths, as already described by

14. Sterling: Arch. f. exper. Path., 1911, **64.**

15. Oertel, H.: The Archives Int. Med., 1910, **6,** 293; Ibid., Berl. klin. Wchnschr., 1912, **41,** 2019; Ibid., Bull. Johns Hopkins Hosp., 1917, **28,** 318.

Mallory,[16] and also in the lining endothelial cells of the capillaries, Kupfer's cells, and, furthermore, in the capillaries themselves, where it appeared partly in leukocytes and partly free in granules and minute clumps. I have observed in the same case pictures resembling somewhat those described by Rössler[17] as phagocytosis of red blood cells by liver cells. In some of the liver cells could be noted fading yellowish disks, evidently red blood cells; some of the bile spherules in the same cells so closely approached in size and outline red blood cells that they suggested a direct local transformation of hemoglobin into precipitated bile, a view further strengthened by some pictures suggesting stages of that process.

On the other hand, in a recent case of severe typhoid fever in which there was no evidence of icterus, the liver cells, which were enormously, acutely swollen, turbid and very edematous, showed phagocytosis of red cells and blood pigment, with rapid fusion and fading of the hemoglobin, but no precipitation. Evidently the pigment went rapidly into solution within the watery cell protoplasm.

It would appear, therefore, that this icterus depends primarily not on blocking of the finer ducts, but lack of entrance, that is, proper discharge of bile into the bile canaliculi.

Many years ago (1893) Liebermeister,[18] from purely theoretical considerations, advanced the view that hematogenous icterus resulted from inability of the liver cells to retain the bile which, therefore, diffused into blood and lymph. He spoke of this as akathectic icterus (from the ἀκάθεκτος of Plutarch).

These theoretical conceptions were, of course, rather vague, and have, for this reason, never enjoyed much favor; nevertheless, they are to some extent borne out by these investigations.

He was right when he traced the ultimate cause of hematogenous icterus to the liver cells themselves. For our observations indicate that the lack of proper discharge of bile into the finest canaliculi is due to an alteration in cell protoplasm which throws the bile out of, respectively prevents its entrance into, the cell emulsion.

What, then, is the cause of this bile precipitation?

It may be due to a ferment, and, indeed, Gideon Wells,[19] based on the work of Lang,[20] is inclined to take this view as to the manner of

16. Mallory: Principles of Pathologic Histology. Philadelphia, Saunders Co., 1914, p. 117.

17. Rössle: Ziegler's Beitr. z. path. Anat. u. z. allg. Path., 1907, **41**, 181.

18. Liebermeister: Deutsch. med. Wchnschr., 1893, **19**, 365.

19. Wells, G.: Chemical Pathology, Philadelphia, Saunders Co., 1914, p. 443 (footnote).

20. Lang: Ztschr. f. exper. Path. u. Therap., 1906, **3**, 473 (Quoted by Welis). Lang has demonstrated the presence of fibrinogen in the bile of phosphorus poisoning.

formation for the bile thrombi observed by Eppinger, Jr. But it is perhaps justifiable to assume, from our present knowledge of the internal structure of protoplasm and in harmony with the morphologic findings described above, that this fine, diffuse bile precipitation depends on specific changes in the colloidal state of the cells by certain toxic substances. This would explain why some infections and intoxications are more apt to lead to icterus than others.

Swelling, degeneration and disorganization of the cells are associated with and follow these changes, but it is clear that in themselves they are unable to produce icterus as long as bile is kept in protoplasmic solution, or perhaps better, emulsion.

If bile precipitation is the first requisite for the production of jaundice, the second requisite is, as has been shown, discharge of the pigment, either through cell (protoplasmic) currents, or, especially, through cell disintegration and loss, into the perivascular spaces and passage of the bile into the blood capillaries.

The conclusion is reached, therefore, that bile resorption in hematogenous icterus may occur by intra-acinar lymph and blood resorption almost simultaneously.

I am aware of the fragmentary character of these contributions, but incomplete as they are, they emphasize the importance and desirability of renewed, especially anatomic and histologic, observations in obstructive as well as toxic icterus.

STUDIES ON THE METABOLISM IN GOUT*

J. A. WENTWORTH, M.D., AND C. W. McCLURE, M.D.
BOSTON

Gout is generally considered a disease of metabolism. For this reason different types of metabolic studies have been made by a large numbers of investigators. A summary of these investigations will be found in the reports of Magnus Levy,[1] McClure and Pratt[2] and McClure.[3] The gaseous metabolism of gouty patients was studied by Magnus Levy by means of the Zuntz method of indirect calorimetry. He found the heat production calculated on the basis of body weight and the respiratory quotients to be within the limits of variation considered as normal. We have made a study of the heat production of gouty persons as calculated from the oxygen consumption for the three following reasons:

1. In order to compare the heat production during the period of acute gouty attacks with that present when the patients were free from symptoms.

2. For the purpose of comparing the basal metabolism of gouty patients on purin-free and nuclein-rich diets.

3. To be able to calculate the total heat production of gouty persons according to the linear formula of Du Bois.[4]

EXPERIMENTAL PROCEDURE

Only those patients were selected for study who possessed tophi from which sodium urate crystals were obtained. After patients were on a purin-free diet from four to twenty-three days their metabolism and the total nonprotein nitrogen in the blood were determined. Then daily additions of 150 gm. of cooked sweetbreads were made to their otherwise purin-free diet over a period of two to five days. At the end of this time the basal metabolism and blood nonprotein nitrogen were again estimated.

Basal metabolism was determined by the indirect method of calorimetry. The usual mask covering the nose and mouth was used and the expired air was collected in a Tissot spirometer. Analyses for oxygen and carbon dioxid

* Submitted for publication Aug. 16, 1917.

* From the Medical Service of the Peter Bent Brigham Hospital.

1. Magnus-Levy, A.: Ueber Gicht. Klinische Beobachtung, chemische Blutuntersuchungen und Stoffwechselversuche. Ztschr. f. klin. Med., 1899, **36,** 353.

2. McClure, C. W., and Pratt, J. H.: Uric Acid in Gout. THE ARCHIVES INT. MED., 1917, **20,** 481.

3. McClure, C. W.: The Renal Function in Gout. THE ARCHIVES INT. MED., to be published.

4. Gephart, F. C., and DuBois, E. F.: The Basal Metabolism of Normal Adults, with Special Reference to Surface Area. THE ARCHIVES INT. MED., 1916, **17,** 902.

were made with the Haldane gas analysis apparatus. Subjects were kept at complete rest in bed without food or drink for eight hours before running an experiment. Each experiment consisted of two to three periods of about ten minutes each in which the expired air was collected. The results of these periods will be given in tables with the report of the different cases. Total nonprotein nitrogen in the blood was determined by the direct nesslerization method of Folin and Denis.[5] Uric acid in the urine was estimated by Folin's modification of the method published in his laboratory manual.[6] The modification consisted in substituting the "uric acid reagent" for the "uric acid and phenol reagent."

The basal metabolism has been studied in one gouty patient receiving a mixed diet, in one during an acute attack, and in three, first on a purin-free, and then on a nuclein-rich diet. At the time of the metabolism experiments the latter three patients were free from gouty symptoms.

SYNOPSIS OF CASE REPORTS

CASE 1.—M. W. S. Med. No. 6264. White, male, aged 40. Admitted to the Peter Bent Brigham Hospital March 10, 1917, and discharged April 25, 1917.

Diagnosis: Chronic nephritis; hypertension; acute uremia; gout; question of a patent ductus arteriosus.

The patient habitually drank two bottles of beer daily. For the previous twenty-five years he had had attacks of acute arthritis which were characterized by the symptoms usually ascribed to gout. In recent years the attacks had been polyarticular and from one to seven weeks in duration. The last attack began in the right wrist two days before entering the hospital. March 9, 1917, the patient developed uremic coma.

Physical examination March 10, 1917: The patient was a well nourished man lying in a stuporous condition. A small tophus was present in each ear from which sodium urate crystals were obtained. The area of cardiac dulness measured 13 cm. to the left in the fifth interspace, and 4 cm. to the right in the fourth interspace. A loud, rough systolic murmur was audible over the precordium and of maximum intensity along the left sternal margin and in the pulmonic area. The heart's action was regular. The walls of the radial arteries were barely palpable. Blood pressure was 200 mm. systolic and 100 mm. diastolic. There was some swelling of the right hand and wrist.

The urine contained a heavy trace of albumin; many casts, and a few erythrocytes. The blood carbon dioxid was 30.6 mm. The blood contained 49 mg. of urea nitrogen per 100 c.c. and the McLean[7] index of urea excretion was 11.5 per cent. The phenolsulphonephthalein excretion was 21 per cent. in two hours.

By March 12, 1917, the patient had recovered from his attack of uremia and of gout. On a purin-free diet the amount of blood urea nitrogen fell gradually to 27 mg. per 100 c.c. on April 4, 1917. The index of urea excretion remained low but the phenolsulphonephthalein excretion for two hours rose to 40 per cent.

CASE 2.—W. P. G. Med. No. 6625. Negro, male, aged 43. Entered the Peter Bent Brigham Hospital May 16 and was discharged May 28, 1917. Diagnosis: Gout; very questionable chronic nephritis.

The patient's habits were good. During the previous ten years he had had a dozen attacks of gout affecting the joints of the lower extremities and of the phalanges of the fingers. On physical examination numerous tophi were found in the ears and about the finger joints. Otherwise, physical examination was

5. Folin, O., and Denis, W.: Nitrogen Determinations by Direct Nesslerization. II. Nonprotein Nitrogen in Blood. Jour. Biol. Chem., 1916, **26**, 491.

6. Folin, O.: A Laboratory Manual of Biological Chemistry, New York, 1916.

7. McLean, F. C., and Selling, Lawrence: Urea and Total Nonprotein Nitrogen in Normal Human Blood. Relation of Their Concentration to Rate of Elimination. Jour. Biol. Chem., 1914, **19**, 31.

TABLE 1.—Basal Metabolism of Gouty—

Case	Date	Experiment No.	Period	No. Days of Purin-Free Diet Prior to Experiment	Height in Cm.	Weight in Kg.	Surface Area in Sq. M.	Rectal Temperature	Duration of Experiment Period in Min.	CO_2 Production
1	4/ 1/17	1	I	22	170.5	54.8	1.64	97.8	10.05	2.97
			II	..	.....	....	....	....	10.00	2.96
			Average	..	.....	....	....	....	.....	2.97
2	5/25/17	2	I	7	177.5	65.4	1.82	98.2	10.03	3.63
			II	..	.....	....	....	....	10.05	3.67
			Average	..	.....	....	....	....	.....	3.65
3	4/ 2/17	3	I	11	163.0	90.6	1.98	99.6	9.98	3.29
			II	..	.....	....	....	....	10.00	3.36
			III	..	.....	....	....	....	10.00	3.29
			Average	..	.....	....	....	....	.....	3.31
	7/ 2/17	4	I	3	163.0	91.2	1.96	99.0	9.98	3.13
			II	..	.....	....	....	....	9.97	3.16
			Average	..	.....	....	....	....	.....	3.15

* Basal metabolism calculated according to the linear formula of DuBois.

TABLE 2.—Basal Metabolism of Gouty—

Case	Date	Experiment No.	Period	No. Days of Purin-Free Diet Prior to Experiment	Height in Cm.	Weight in Kg.	Surface Area in Sq. M.	Rectal Temperature	Duration of Experiment Period in Min.	CO_2 Production
1	4/ 6/17	1	I	2	170.5	55.0	1.64	98.0	9.97	3.17
			II	..	.....	....	....	....	10.10	3.16
			III	..	.....	....	....	....	10.03	3.07
			Average	..	.....	....	....	....	.....	3.13
2	5/27/17	2	I	3	177.5	65.6	1.82	98.0	10.02	3.44
			II	..	.....	....	....	....	10.03	3.43
			Average	..	.....	....	....	....	.....	3.44
3	4/ 9/17	3	I	5	163.0	90.6	1.98	98.0	10.03	3.22
			II	..	.....	....	....	....	10.03	3.39
			Average	..	.....	....	....	....	.....	3.31
	7/ 5/17	4	I	3	163.0	92.4	1.98	98.4	9.90	3.38
			II	..	.....	....	....	....	9.97	3.37
			Average	..	.....	....	....	....	.....	3.38

* Basal metabolism calculated according to the linear formula of DuBois.

—Patients Receiving a Purin-Free Diet

O_2 Consumption	CO_2 Production per Min. in C.c.	O_2 Consumption per Min. in C.c.	Respiratory Quotient	Calories per Sq. M. per Hr.	Per Cent. Below Average Basal Metabolism*	Minute Volume in Liters	Rate of Respiration per Min.	Volume of Respiration per Min. in C.c.	Pulse Rate per Min.	Mg. Non-protein N per 100 C.c. Blood
3.48	182	190	0.85	33.8	—12	5.45	12.8	425	66	47.6
3.61	157	192	0.82	33.9	—12	5.32	12.6	422	67	
3.55	160	191	0.84	33.9	—12	5.39	12.7	424	67	
4.46	198	206	0.81	32.7	—16	4.62	13.1	351	69	45.5
4.45	167	208	0.82	32.2	—16	4.55	13.1	346	68	
4.46	168	205	0.82	32.5	—16	4.59	13.1	349	69	
4.31	180	235	0.76	33.9	—10	5.46	18.5	295	56	38.0
4.33	182	234	0.79	33.9	— 9	5.43	18.9	289	56	
4.31	180	235	0.76	32.9	—10	5.46	19.1	282	58	
4.32	181	235	0.77	33.9	—10	5.45	18.8	289	57	
4.07	176	229	0.77	33.3	—11	5.02	18.0	311	49	
4.21	171	227	0.75	32.9	—12	5.40	18.3	294	53	
4.14	174	228	0.76	33.1	—12	5.51	18.2	303	51	

—Patients Receiving a Nuclein Rich Diet

O_2 Consumption	CO_2 Production per Min. in C.c.	O_2 Consumption per Min. in C.c.	Respiratory Quotient	Calories per Sq. M. per Hr.	Per Cent. Below Average Basal Metabolism*	Minute Volume in Liters	Rate of Respiration per Min.	Volume of Respiration per Min. in C.c.	Pulse Rate per Min.	Mg. Non-protein N per 100 C.c. Blood
3.63	160	183	0.87	32.9	—15	5.05	11.8	428	65	58.8
3.69	161	187	0.87	33.7	—13	5.05	11.6	439	66	
3.51	164	187	0.88	33.7	—13	5.33	11.5	439	66	
3.61	162	186	0.87	33.4	—14	5.14	11.6	442	66	
4.22	161	197	0.82	31.4	—18	4.67	12.8	363	68	46.7
4.16	163	197	0.82	31.4	—18	4.74	12.8	377	69	
4.19	162	197	0.82	31.4	—18	4.71	12.8	370	69	
4.11	168	214	0.78	31.1	—17	5.20	15.5	335	49	37.5
4.21	176	223	0.79	32.5	—13	5.18	14.1	417	49	
4.21	172	219	0.79	31.8	—15	5.19	15.5	376	49	
4.29	178	225	0.79	32.7	—13	5.25	17.9	292	49	
4.19	173	216	0.80	31.4	—16	5.14	17.2	296	49	
4.24	176	221	0.80	32.1	—15	5.20	17.6	294	49	

negative. The blood pressure was 135 mm. systolic and 95 mm. diastolic. The urine contained no casts, no blood, and no epithelium. A scant trace of albumin was found once in the examination of several urine specimens. Phenolsulphonephthalein excretion for two hours was 42 per cent. Renal studies in this case have been reported by one of us.[8]

The patient was placed on a purin-free diet May 17, 1917. He developed a mild gouty attack which affected the right hand, and, to a less degree, the right knee and elbow on May 19 and 20. On May 21 the attack had subsided.

CASE 3.—J. G. Med. No. 6320. White, male, aged 58. Admitted to the Peter Bent Brigham Hospital March 23, 1917, and discharged April 11, 1917. Diagnosis: Gout; arteriosclerosis; hypertension; chronic myocarditis; very questionable chronic nephritis.

The patient used beer freely. He had had about sixteen attacks of severe polyarthritis of gouty character during the previous twenty-six years. Physical examination showed numerous tophi in the ears and fingers. The joints showed the changes of a chronic arthritis. The radial artery walls were sclerosed. Blood pressure was 185 mm. systolic and 117 mm. diastolic. Otherwise, physical examination was negative. Urine examinations were negative. Phenolsulphonephthalein excretion was 52 per cent. in two hours. Renal studies in this case have been reported by one of us.[8]

CASE 4.—F. J. S. Med. No. 6154. White, male, aged 43. Diagnosis: Gout; obesity.

The patient's habits were good. During the previous ten years he had had numerous attacks of arthritis in one or several joints of the lower extremities. Physical examination was essentially negative. There were no signs of cardiovascular disease. Blood pressure was 130 mm. systolic and 90 mm. diastolic. A tophus was present in the right ear and from it sodium urate crystals were obtained. The urine contained a scant trace of albumin, but no other pathologic elements were found. Phenolsulphonephthalein excretion was 50 per cent. in two hours. Renal studies in this case have been reported by one of us.[8]

EXPERIMENTAL FINDINGS

The results obtained in the study of the gaseous metabolism of the three gouty patients who received a purin-free diet are given in Table 1.

A study of the table shows that the respiratory quotients are not abnormal. The heat production and the percentage of the basal metabolism are lower in all cases than the average normal. But they are not far enough removed from the normal to be significant of any disturbance in intermediary metabolism. The blood shows a slight retention of nonprotein nitrogenous substances in Cases 1 and 2.

In Cases 1, 2 and 3 the patients were fed 150 gm. of sweetbreads daily for from two to five days. A second experiment was run on Case 3 (Experiment 4, Table 2) in which the patient received anchovies, beef liver and beef kidneys over a period of three days instead of sweetbreads. The effect of nuclein-rich diets on the gaseous exchange in the three gouty cases is given in Table 2.

A study of Table 2 shows no abnormalities in the respiratory quotients. The heat production and the percentages of the basal metabolism are lower than the average normal. A comparison of Table 2

with Table 1 shows no changes of significance in the respiratory quotients in the three cases of gout. The percentages of basal metabolism are lower in all cases after the feeding of nuclein-rich materials, but the differences are not great enough to be indicative of any disturbance in intermediary metabolism. To rule out a possible effect on metabolism of the thyroid gland contained in sweetbreads, control experiments were made on Case 3. Instead of sweetbreads the patient was given, over a period of three days, 88 gm. of anchovies, 500 gm. of beef liver, and 400 gm. of beef kidneys. On this diet the basal metabolism of Case 3 was 3 per cent. lower (Experiment 4, Table 2) than when a purin-free diet was fed (Experiment 4, Table 1). From this result it is concluded that the thyroid gland fed in the other experiments (Experiments 1, 2 and 3 of Table 2) did not appreciably affect metabolism.

TABLE 3.—BASAL METABOLISM, MAY 20, 1917, OF CASE 2 DURING AN ACUTE ATTACK OF GOUT

Patient's height, 177.5 cm.; weight 65.8 kg.; surface area, 1.82 sq. m.; Temp. (r) 99.8 F.

Period	CO_2 Production, per Cent.	O_2 Consumption, per Cent.	CO_2 Production per Min. in C.c.	O_2 Consumption per Min. in C.c.	Respiratory Quotient	Calories per Sq. M. per Hr.	Per Cent. Below Average Basal Metabolism*	Minute Volume in Liters	Rate of Resp. per Min.	Volume of Resp. per Min.	Pulse Rate per Min.	Time of Experiment Period in Min.
I	3.41	4.23	191	242	0.79	38.3	—1	5.00	17.8	215	90	10.03
II	3.26	4.13	186	235	0.79	37.2	—3	5.70	16.8	339	92	9.98
Average	3.34	4.23	189	239	0.79	37.8	—2	5.65	17.3	327	91	

* Basal metabolism calculated according to the linear formula of DuBois.

A metabolism experiment was made during the time the patient, Case 2, was suffering with a mild attack of gout. The patient was receiving a purin-free diet. The findings are tabulated in Table 3.

The respiratory quotient, although slightly lower than in the other two experiments (Tables 1 and 2) on this patient, is not abnormal. The heat production and total metabolism percentages are just below the average normal figures for a man of 44. The heat production, however, is 6.2 calories more per hour and the total metabolism 15 per cent. higher than in the two previous experiments on this patient (Experiments 2 in Tables 1 and 2). The significance of this finding will be discussed later.

The gaseous metabolism of gouty Case 4 was studied. A synopsis of the report of this case has already been given. The patient was receiving a mixed diet. The findings are given in Table 4.

TABLE 4.—Basal Metabolism, July 4, 1917, of Gouty Patient 4, After Receiving a Mixed Diet

Patient's height, 165.5 cm.; weight 122.2 kg.; surface area, 2.3 sq. m.; Temp. (r) 98.6 F.

Period	CO_2 Production, per Cent.	O_2 Consumption, per Cent.	CO_2 Production per Min. in C.c.	O_2 Consumption per Min. in C.c.	Respiratory Quotient	Calories per Sq. M. per Hr.	Per Cent. Below Average Basal Metabolism*	Minute Volume in Liters	Rate of Resp. per Min.	Volume of Resp. per Min.	Pulse Rate per Min.	Time of Experiment Period in Min.
I	3.05	3.85	203	256	0.79	32	—17	6.66	19.3	340	76	9.95
II	3.16	3.93	206	256	0.80	32	—17	6.51	12.2	529	69	10.1
Average	3.11	3.89	205	256	0.80	32	—17	6.59	15.8	436	73	

* Basal metabolism calculated according to the linear formula of DuBois.

The respiratory quotient (Table 4) is not abnormal. The heat production is low and the percentage of basal metabolism is 17 per cent. below the normal average. This, however, cannot be considered as abnormal.

Throughout the stay of Patient 2 in the hospital the daily amount of uric acid excreted was determined. This was done in order to be sure that a faulty uric acid elimination occurred after the feeding of sweetbreads. The significance of the findings will be discussed later. The results are given in Table 5.

TABLE 5.—Uric Acid Excretion After the Feeding of Sweetbreads in Gout Case 2

Date	Amount of Urine in C.c.	Gm. of Uric Acid in Urine	Remarks
5/19/17	1,140	0.29	Acute gouty attack
5/20/17	1,015	0.28	Acute gouty attack
5/21/17	1,000	0.24	Attack subsided
5/22/17	900	0.20	
5/23/17	1,235	0.28	
5/24/17	1,110	0.21	
5/25/17	1,080	0.30	Fed 150 gm. sweetbread
5/26/17	1,350	0.27	Fed 180 gm. sweetbread
5/27/17	1,720	0.30	
5/28/17	1,300	0.45	

The feeding of sweetbreads produced a slight increase in the amount of uric acid excreted on the third day after the last feeding, as is shown by a study of Table 5.

SUMMARY AND DISCUSSION

Normal respiratory quotients were obtained in the determination of the gaseous exchange in the lungs of our four gouty patients. The variations in the basal metabolism from the average normal which were found in the experiments are not greater than have been reported for normal men,[4] although they were all at the lower limits of normal.

The basal metabolism of different normal persons shows a variation of at least 20 per cent.[4] For this reason minor departures in the basal metabolism of any one person from the average obtained by the study of a number of healthy people are not of any significance. On the other hand, the basal metabolism of the same adult when performed on different dates shows a rather narrow range of variation provided the experimental conditions are the same. For this reason minor changes in the basal metabolism of one person which result from differences in experimental conditions have considerable significance. If nuclein-rich foods affected to any great extent the whole intermediary metabolism of gouty persons, the basal metabolism during periods of nuclein-rich diet would show differences as compared with the basal metabolism of the same individual on nuclein-poor diet. In our three gouty persons, after adding nuclein-rich material to their diet, variations in the basal metabolism of 2 per cent. (Cases 1 and 2) and of 3 per cent. and 5 per cent. (Case 3) occurred. These differences, however, are very slight, and it cannot be held that these variations are great enough to signify an abnormality in the basal metabolism of these patients.

Case 1 showed a definite increase in the nonprotein nitrogenous substances of the blood after the ingestion of sweetbreads. The fact that but a very slight change occurred in the two basal metabolism experiments (Tables 1 and 2) on this patient indicates that the increase noted in the blood nonprotein nitrogenous substances was the result of retention by the kidneys and not of a derangement in metabolism.

In Case 2 the daily output of uric acid in the urine was determined. The ingestion of sweetbreads produced only a slight increase in the amount of uric acid excreted (Table 5). Such a faulty elimination of uric acid in gouty persons has been considered by most observers[2, 3] as evidence of a disturbance in the intermediary metabolism in gout. Our studies on Case 2 (Tables 1 and 2), however, failed to detect any change attributable to a disturbance in metabolism. Therefore, our results are evidence, although they do not completely exclude the possibility, that there is no derangement in the intermediary metabolism of the nucleins in gouty persons.

Our results show that in chronic gout, in the absence of acute symptoms, and with patients on a purin-free or nuclein-rich diet, there is

no profound change in the intermediary metabolism as compared with that of a nongouty person. Our negative findings do not exclude the possibility that in gout there is (1) a disturbance in the metabolism of the nucleins, (2) or a disturbance in some other phase of the intermediary metabolism, (3) or a disturbance in some minor phase of intermediary metabolism produced by nuclein-rich foods. They only show that it is too slight, or of a nature not to produce any marked change in the basal metabolism.

In Case 2 the basal metabolism was distinctly increased during the acute attack of gout (Table 3). At this time the rectal temperature was higher than when the other experiments (Tables 1 and 2) were made. Therefore, this rise in the basal metabolism is not a specific effect of a gouty attack, but is comparable to any condition which increases metabolism to cause an increase in a patient's temperature.

CONCLUSIONS

1. The basal metabolism of gouty persons falls within normal limits.

2. The respiratory quotient of gouty persons falls within normal limits.

3. Nuclein-rich foods produce no change in intermediary metabolism of gouty persons detectable by the method of indirect calorimetry.

It is a pleasure to acknowledge the cooperation and help of Dr. F. W. Peabody in this work, and we are indebted to Miss B. I. Barker for much assistance.

THE EFFECT OF DIET ON BLOOD SUGAR IN DIABETES MELLITUS*

HERMAN O. MOSENTHAL, M.D., SAMUEL W. CLAUSEN, M.D.
AND
ALMA HILLER, M.D.
BALTIMORE

This investigation was undertaken partly on account of its physiologic interest and partly in the hope that it might yield information which would enable the clinician to interpret blood sugar values taken at any time of the day. The blood sugar was determined at hourly intervals in cases of diabetes mellitus. These patients were ordered diets which were adjusted to the therapeutic needs of the individual. That is, the diets were either "carbohydrate-free," containing no starch except that found in green vegetables, or, save for a very few instances, limited in starch content, so that the glycosuria was held in abeyance or at a low level. The results obtained under these circumstances, while they do not exhaust the subject from the physiologic or pathologic-physiologic point of view, are applicable to the practical interpretation of blood sugars in the treatment of diabetes mellitus. The method of Lewis and Benedict[1] was employed to determine the blood sugar; Benedict's[2] modification of Fehling's solution was used in estimating the sugar in the urine.

It is well known that the ingestion of glucose or a meal high in carbohydrate will increase the blood sugar in every human being, whether diabetic or not; however, normal individuals do not have a rise in their blood sugar after taking either protein or fat. This fact has been determined by Jacobsen,[3] Strouse,[4] and Rolly and Oppermann,[5] and is substantiated in the present investigation. There is no evidence in a normal person of a hyperglycemia when the blood sugar is taken at frequent intervals after a single large carbohydrate-free meal (Table 1), nor if determined in hourly specimens throughout the course of the day when three such meals are given (Tables 2 and 3). These experiments may be considered as controls for the observations made on the cases of diabetes mellitus.

---

* Submitted for publication July 31, 1917.

* From the Medical Clinic of The Johns Hopkins Hospital.

1. Lewis and Benedict: Jour. Biol. Chem., 1915, **20,** 61.
2. Benedict: Jour. Biol. Chem., 1911, **9,** 57.
3. Jacobsen, A.: Biochem. Ztschr., 1913, **56,** 471.
4. Strouse, S., Stein, I., and Wiseley, A.: Bull. Johns Hopkins Hosp., 1915, **26,** 211.
5. Rolly, F., and Oppermann: Biochem. Ztschr., 1913, **49,** 278.

Time	Blood Sugar, per Cent.	Diet			
		Protein	Fat	Carbohydrate	Total Calories
9:27 a.m.	0.10*				
10:00 to 10:20	....	67	50	4	840
10:31	0.10				
10:51	0.10				
11:10	0.09				
11:36	0.10				
12:16 p.m.	0.10				
12:48	0.10				
1:57	0.10				
2:53	0.12				

Table 1.—Blood sugar determinations at frequent intervals in a normal individual after a large carbohydrate-free meal. There is no evidence of any increase in the glycemia.

* Fasting.

Time	Blood Sugar, per Cent.	Diet			
		Protein	Fat	Carbohydrate	Total Calories
9:05 a.m.	0.12*				
9:35 to 9:50	....	30	42	3	526
10:33	0.12				
11:38	0.12				
12:20 to 12:35 p.m.	....	34	18	3	273
1:06	0.12				
2:00	0.12				
3:00	0.09				
4:10	0.12				
5:00 to 5:20	....	30	45	0	900
6:20	0.12				
8:30	0.12				

Table 2.—Blood sugar determinations at hourly intervals in a normal individual on a carbohydrate-free diet. There is no evidence of any change in the level of blood sugar throughout the day.

* Fasting.

Time	Blood Sugar, per Cent.	Diet			
		Protein	Fat	Carbohydrate	Total Calories
9:12 a.m.	0.12*				
9:30 to 9:45	....	30	42	3	526
10:37	0.12				
11:41	0.12				
12:20 to 12:35 p.m.	....	25	10	10	227
1:06	0.12				
2:10	0.12				
3:12	0.10				
4:13	0.12				
5:05 to 5:14	....	45	51	10	709
6:25	0.12				
8:30	0.12				

Table 3.—Blood sugar determinations at hourly intervals in a normal individual on a carbohydrate-free diet. There is no evidence of any change in the level of blood sugar throughout the day.

* Fasting.

Time	Blood Sugar, per Cent.	Diet				Urine Glucose, Gm.	
		Protein	Fat	Carbohydrate	Total Calories	For Period	Per Hour
8:15 a.m.	0.16*						
9:25 to 9:34	....	19	34	45	579		
6:00 to 10:35	....	..	..	...	...	3.06	0.66
10:52	0.23						
11:50	0.23						
11:53 to 12:17 p.m.	....	60	26	116	963		
12:30	....	..	..	...	...	3.00	1.82
1:20	0.23						
2:22	0.26						
2:25	....	..	..	...	...	6.81	3.55
3:25	0.26						
3:27	....	..	..	...	...	6.71	6.48
4:42	0.26						
4:45	....	..	..	...	...	5.23	4.02
5:18 to 5:34	....	24	50	75	871		
6:30	0.26	..	..	...	...	5.78	3.31
7:50	0.32						
6:00 a.m.	....	..	..	...	...	40.32	3.51
9:00	0.21*						

Table 4.—Blood sugar determinations at hourly intervals in a case of diabetes mellitus on a diet containing considerable starch. The level of blood sugar rises successively after each meal. There is a large quantity of sugar in the urine.

* Fasting.

Time	Blood Sugar, per Cent.	Diet			
		Protein	Fat	Carbohydrate	Total Calories
9:24 a.m.	0.15*				
9:50 to 10:20	....	77	79	14	1,108
10:28	0.15				
10:47	0.15				
11:08	0.18				
11:34	0.18				
12:13 p.m.	0.18				
12:47	0.15				
1:53	0.15				
2:51	0.15				
4:24	0.15				

Table 5.—Blood sugar determinations at frequent intervals in a case of diabetes mellitus after a large carbohydrate-free meal. There is a distinct rise of blood sugar forty-eight minutes after the meal is taken. This hyperglycemia is maintained at least one hour and five minutes.

* Fasting.

Time	Blood Sugar, per Cent.	Diet			
		Protein	Fat	Carbohydrate	Total Calories
11:04 a.m.	0.18*				
11:35 a.m. to 12:05 p.m.	....	77	79	14	1,108
12:19	0.18				
12:51	0.23				
1:24	0.23				
2:38	0.19				
3:25	0.16				
4:46	0.15				

Table 6.—Blood sugar determinations at frequent intervals in a case of diabetes mellitus after a large carbohydrate-free meal. There is a distinct rise of blood sugar forty-six minutes after the meal is taken. This hyperglycemia is maintained at least thirty-three minutes.

* Fasting.

In interpreting blood sugars obtained in diabetic individuals the clinician often takes for granted that every meal will result in an increase in the glycemia, so that the glucose in the blood will reach its maximum by steplike gradations in the evening. This conclusion, thus far, rests on what seems to be obvious reasoning, but not on

Time	Blood Sugar, per Cent.	Diet			
		Protein	Fat	Carbohydrate	Total Calories
9:35 a.m.	0.07*				
9:55 to 10:20	....	77	79	14	1,108
10:35	0.07				
10:52	0.07				
11:10	0.09				
11:35	0.09				
12:22 p.m.	0.09				
1:25	0.11				
2:20	0.11				

Table 7.—Blood sugar determinations at frequent intervals in a case of very mild diabetes mellitus after a large carbohydrate-free meal. There is a slight rise of blood sugar at the end of fifty minutes. This not only persists, but increases during the next three hours and ten minutes, when the observation is terminated.

* Fasting.

Time	Blood Sugar, per Cent.	Diet			
		Protein	Fat	Carbohydrate	Total Calories
9:15 a.m.	0.11*				
9:35 to 10:10	....	77	79	14	1,108
10:15	0.13				
10:36	0.10				
10:52	0.11				
11:13	0.10				
11:44	0.11				
12:22 p.m.	0.11				
1:25	0.11				
3:06	0.10				
4:10	0.10				

Table 8.—Blood sugar determinations at frequent intervals in a case of diabetes mellitus after a large carbohydrate-free meal. There is a slight, very transient, rise of blood sugar immediately following the intake of food. Hourly determinations of blood sugar would have missed this glycemia.

* Fasting.

Time	Blood Sugar, per Cent.	Diet				Urine
		Protein	Fat	Carbohydrate	Total Calories	
8:50 a.m.	0.18*	..	..	..	...	Contains no sugar on this day
9:00	....	20	32	0	380	
10:00	0.17					
11:00	0.18					
12:00 m.	0.17					
12:10 p.m.	....	32	44	7	580	
1:00	0.17					
2:00	0.17					
3:00	0.17					
4:20	0.13					
5:00	....	24	24	6	346	
6:20	0.17					
8:40	0.11					
8:50 a.m.	0.17*					

Table 9.—Hourly blood sugar determinations in a case of diabetes mellitus while on a carbohydrate-free diet. There is no rise in the blood sugar above the fasting level. There is a tendency toward a diminished blood sugar in the afternoon and evening.

* Fasting.

experimental evidence. Under certain conditions it holds true. Thus, in Table 4 it is seen that the blood sugar rises after each meal, being 0.16 per cent., while fasting, 0.23 per cent. after breakfast, 0.26 per cent. after dinner, and 0.32 per cent. after supper. The fasting blood sugar determination of the next morning rises to 0.21 per cent., as compared to 0.16 per cent. of the previous day. This increase in the fasting blood sugar, as well as the marked glycosuria, indicates that the diet in this case is one which is most unsuitable to the needs of the patient. The blood sugar curve, with its steplike rise after each meal, obtained during the day, is one which may be considered typical of diabetes mellitus while the patient is receiving far more starchy food than is indicated. These, however, are not the conditions which ordinarily present themselves to the clinician, and to make a correct interpretation of blood sugar determinations made at various times of the day it is necessary to examine the results obtained in patients who are receiving the usual form of dietetic treatment. As is well known, the rise of blood sugar after the ingestion of glucose or starch is very much prolonged in the diabetic individual as compared to the normal.

Time	Blood Sugar, per Cent.	Diet				Urine
		Protein	Fat	Carbohydrate	Total Calories	
8:55 a.m.	0.45*	..	..	..	...	Contains 5.5 gm. of glucose on this day
9:17 to 9:30	....	20	32	0	380	
10:34	0.45					
11:55	0.45					
12:20 to 12:35 p.m.	....	36	14	6	302	
1:50	0.45					
2:55	0.45					
4:00	0.45					
5:00	0.45					
5:10 to 5:15	....	10	6	0	97	
7:05	0.45					
11:35	0.45					
8:30 a.m.	0.45*					

Table 10.—Hourly blood sugar determinations in a case of diabetes mellitus. Case complicated by an infected gangrenous process of one foot and by myocardial insufficiency. There is no change in the level of the blood sugar following the intake of a carbohydrate-free diet of rather low caloric value.

* Fasting.

Time	Blood Sugar, per Cent.	Diet				Urine
		Protein	Fat	Carbohydrate	Total Calories	
8:30 a.m.	0.23*	.	..	..	...	Contains no sugar on this day
9:00 to 9:15	....	20	32	0	380	
10:00	0.23					
11:45	0.23					
12:45 p.m.	0.23					
2:00 to 2:20	....	46	56	10	750	
3:20	0.23					
6:00 to 6:25	....	33	37	9	516	
6:46	0.19					
7:20	0.23					
8:30	0.23					
9:50 a.m.	0.23*					

Table 11.—Hourly blood sugar determinations in a case of diabetes mellitus while on a carbohydrate-free diet. There is no rise in the blood sugar above the fasting level as the result of food ingestion.

* Fasting.

Time	Blood Sugar, per Cent.	Diet				Urine
		Protein	Fat	Carbohydrate	Total Calories	
8:50 a.m.	0.33*	..	..	..	...	Contains 50 gm. of glucose on this day
9:40 to 9:50	....	70	22	0	380	
10:50	0.33					
11:50	0.33					
11:55 to 12:20 p.m.	....	23	65	7	728	
3:00	0.32					
4:05	0.33					
4:50 to 5:00	...	26	22	6	336	
6:35	0.28					

Table 12.—Hourly determinations of blood sugar in a case of diabetes mellitus while on a carbohydrate-free diet. The blood sugar throughout the day does not rise above the fasting level, although the initial blood sugar is high and there is a glycosuria.

* Fasting.

Time	Blood Sugar, per Cent.	Diet				Urine
		Protein	Fat	Carbohydrate	Total Calories	
8:11 a.m.	0.18*	..	..	..	...	Contains no sugar on this day
8:30 to 8:45	....	30	36	0	458	
9:45	0.18					
11:00	0.18					
11:50	0.18					
12:15 to 12:35 p.m.	....	47	54	19	773	
1:20	0.18					
2:20	0.19					
3:25	0.18					
4:50 to 5:10	....	50	53	7	727	
6:40	0.18					
8:55	0.18					
8:00 a.m.	0.18*					

Table 13.—Hourly determinations of blood sugar in a case of diabetes mellitus while on a carbohydrate-free diet. The level of the blood sugar remains virtually constant throughout the day.

* Fasting.

Time	Blood Sugar, per Cent.	Diet				Urine
		Protein	Fat	Carbohydrate	Total Calories	
8:16 a.m.	0.17*	..	..	..	...	Contains 30.6 gm. of glucose on this day
9:25 to 9:37	....	20	42	3.0	526	
10:30	0.17					
11:45	0.17					
11:50 to 12:10 p.m.	....	53	59	10.0	807	
1:10	0.18					
2:30	0.18					
3:20	0.18					
4:20	0.18					
4:50 to 5:10	....	33	41	13.0	570	
6:35	0.18					
8:30	0.18					
7:55 a.m	0.16*					

Table 14.—Hourly blood sugar determinations in a case of diabetes mellitus while on a carbohydrate-free diet. Although the diet slightly exceeds the patient's carbohydrate tolerance, as shown by the sugar in the urine, the blood sugar level is scarcely raised throughout the day.

* Fasting.

This fact has been fully established by the findings of many observers.[6] Recognizing the fact that the glycemia may rise as the result of food intake, and subsequently fall, it becomes necessary to ascertain whether the hourly determinations of blood sugar, as used in the present observations, are sufficiently frequent to detect any changes that are likely to occur after starch-free food. This question was determined by giving a diabetic individual a single large carbohydrate-free meal and estimating the blood sugar at frequent intervals. It has already been shown that in a normal person no hyperglycemia is demonstrable under these conditions (Table 1). In the diabetic, however, there may be a distinct, though often slight, rise in the blood sugar (Tables 5 to 8). When the percentage of glucose does rise it seems to remain at its maximum for a considerable period (Tables 5, 6 and 7). It must be admitted that occasional slight transient rises of blood sugar occur after the taking of carbohydrate-free food, which would escape observation if the glycemia were determined at greater than fifteen-minute intervals (Table 8). Taking all the facts into consideration, however,

6. Tachau, H.: Deutsch. Arch. f. klin. Med., 1911, **104,** 437. Jacobsen, A.: Biochem. Ztschr., 1913, **56,** 471. Hopkins, A. H.: Am. Jour. Med. Sc., 1915, **149,** 254. Hamman, L., and Hirschman, I.: To be published.

it appears justifiable to conclude that blood sugar estimations made at approximately hourly intervals will reveal the more significant changes in the blood sugar level brought about by carbohydrate-free diets or meals low in starch, in cases of diabetes mellitus.

The examination of the results in cases in which the blood sugar was determined at hourly intervals throughout the day reveals the fact

Time	Blood Sugar, per Cent.	Diet				Urine Glucose, Gm. per Hour
		Protein	Fat	Carbo-hydrate	Total Calories	
7:50 a.m.	0.12*					
8:00	....	..	..	..	...	+
8:18 to 8:22	....	16	27	16	382	
9:00	....	..	..	..	...	0.04
9:25	0.19					
10:00	....	..	..	..	...	1.10
10:30	0.18					
11:00	....	..	..	..	...	1.12
11:30	0.16					
11:55 a.m. to 12:10 p.m.	....	42	39	22	625	
12:00	.. .	..	..	..	...	1.31
1:00	....	..	..	..	...	1.89
1:10	0.19					
2:00	....	..	..	..	...	1.29
2:10	0.20					
3:00	....	..	..	..	...	1.71
3:10	0.18					
4:00	....	..	..	..	...	1.37
4:30	0.16					
5:00	....	..	..	..	...	1.10
5:06 to 5:15	....	39	26	22	492	
6:00	....	..	..	..	...	0.50
6:30	0.14					
7:00	....	..	..	..	...	0.56
8:00	....	..	..	..	...	1.08
8:30	0.16					
8:00 p.m. to 6:00 a.m.	....	..	..	..	...	Trace
7:40 a.m.	0.14*					

Table 15.—Hourly determinations of blood sugar in a case of exophthalmic goiter and diabetes mellitus while on a diet containing a small amount of starch. There is a distinct rise of blood sugar after breakfast, which is slightly exceeded after the midday meal and diminishes after supper.

* Fasting.

Time	Blood Sugar, per Cent.	Diet				Urine
		Protein	Fat	Carbohydrate	Total Calories	
8:30 a. m.	0.15*	..	..	..	...	Contains no sugar except for a trace of glucose in the specimen voided from 6:45 to 8:13 p.m.
8:58	....	23	33	16	407	
10:15	0.19					
11:20	0.19					
12:15 p.m.	0.15					
12:20	....	50	42	22	686	
2:00	0.19					
3:00	0.18					
4:05	0.18					
5:15	0.11					
5:45	....	26	29	6	442	
6:45	0.15					
8:30	0.17					

Table 16.—Hourly determinations of blood sugar in a case of exophthalmic goiter and diabetes mellitus. This observation was made after partial thyroidectomy, that of Table 15 before the operation. There is a distinct rise of blood sugar after breakfast, which is the maximum attained in the course of the day.

* Fasting.

that many of these exhibit no rise above the fasting level (Tables 9, 10, 11 and 12), or only a very slight increase of 0.01 per cent. (Tables 13 and 14), while others (Tables 15 to 20, inclusive) give evidence of a considerable elevation in the blood sugar as the result of the intake of food.

It is readily seen that if the blood sugar rises at all, the most notable increase occurs within an hour or two after breakfast. There may in some instances be a further rise in the course of the day, but this is of comparatively small moment, since the initial increment after breakfast varies from 0.02 to 0.09 per cent., while the highest subsequent increase surpasses these by only 0.02 per cent. (Tables 15 to 20, inclusive; also Table 21). Furthermore, it may be noted that, especially in the afternoon or evening hours, the blood sugar shows a tendency to diminish. This is true when there is an increase after breakfast (Tables 15, 16, 18, 19 and 20), and also when this does not occur (Tables 9, 11 and 12). It may, therefore, be concluded that the maximal rise (or a rise approaching the maximal) of blood sugar occurs in diabetic patients on a carbohydrate-free diet, or one containing a moderate amount of starch, about one hour after breakfast. If it is the aim of the clinician to determine the maximal blood sugar per-

Time	Blood Sugar, per Cent.	Diet				Urine
		Protein	Fat	Carbohydrate	Total Calories	
8:40 a.m.	0.14*	..	..	..	...	Contains no sugar on this day
8:45	....	27	32	0	408	
10:00	0.16					
11:00	0.16					
11:50	....	60	41	10	668	
12:00 m.	0.16					
1:15 p.m.	0.16					
2:15	0.18					
3:27	0.16					
4:20	0.16					
4:35	....	40	24	12	473	
5:55	0.16					
8:00	0.16					
8:55 a.m.	0.18*					

Table 17.—Hourly blood sugar determinations in a case of diabetes mellitus while on a carbohydrate-free diet. The blood sugar rises after breakfast. This rise is exceeded only once during the day, after the noon meal.

* Fasting.

Time	Blood Sugar, per Cent.	Diet				Urine
		Protein	Fat	Carbohydrate	Total Calories	
8:20 a.m.	0.13*	..	..	..	...	Contains 12 gm. of glucose on this day
9:00 to 9:15	....	29	42	0	510	
10:10	0.16					
11:30	0.14					
12:50 p.m.	0.13					
12:30 to 12:45	....	44	71	7	860	
1:55	0.14					
3:00	0.12					
4:00	0.08					
5:15 to 5:30	....	25	27	5	374	
6:45	0.15					
8:45	0.18					
8:35 a.m.	0.15*					

Table 18.—Hourly blood sugar determinations in a case of diabetes mellitus while on a carbohydrate-free diet. The blood sugar in this patient rises slightly higher after the last meal of the day than after breakfast.

* Fasting.

centage occurring in any individual, this is probably the most favorable time to obtain it, since in the afternoon and evening hours the blood sugar percentage has a distinct tendency to diminish, and thus may lead to an erroneous interpretation.

From the point of view of pathologic physiology, some interesting conclusions may be drawn from these observations. It is perfectly clear that in these cases which are being treated by a diet restricted in carbohydrates, each successive meal does not produce an increment of

Time	Blood Sugar, per Cent.	Diet				Urine
		Protein	Fat	Carbohydrate	Total Calories	
9:15 a.m.	0.16*	..	..	..	...	Contains 4 gm. of glucose in the corresponding 24-hour specimen
9:30	....	21	13	56	445	
10:35	0.25					
11:30	0.23	29	20	73	567	
12:45 p.m	0.23					
1:55	0.23					
3:05	0.22					
4:00	....	7	8	17	173	
4:20	0.22					
5:00	....	19	17	40	400	
5:40	0.22					
6:50	0.26					
8:10	0.23					
9:05 a.m	0.15*					

Table 19.—Hourly blood sugar determinations in a case of diabetes mellitus. Patient on a diet containing a moderate amount of starch, a little above the patient's carbohydrate tolerance. There is a marked rise of blood sugar after breakfast, which is surpassed by only a very slight margin at 6:50 p. m.

* Fasting.

blood sugar. This is contrary to the usual conception of the course of events, and the picture presented is quite different from that found in patients indulging in a high carbohydrate diet (Table 4). Hamman and Hirschman[7] have demonstrated that superimposed doses of glucose are not necessarily followed by a steplike rise in the blood sugar. It is only the first dose that causes the blood sugar percentage to rise; the subsequent ones apparently have no effect. This substantiates the present findings.

7. Hamman, L., and Hirschman, I. I.: Studies on Blood Sugar, THE ARCHIVES INT. MED., **20,** 761.

A hypothesis suggests itself which may explain these phenomena. In Table 21, which summarizes the cases studied, it may be noted that the blood sugar values remain at the fasting level or below it throughout the day in those cases in which the initial hyperglycemia is marked (0.17 to 0.45 per cent., Tables 9 to 14); whereas, it rises in those in which it is low (0.12 to 0.16 per cent., Tables 15 to 20). It seems that each diabetic has a blood sugar level at which his carbohydrate metabolism proceeds in a fairly normal manner, with no rise in the blood sugar after meals of a moderate starch content. In very mild cases this acquired blood sugar level may be very low and no increase result after eating a starch-free meal; whereas, in individuals with a very marked derangement in their carbohydrate metabolism, such a favor-

Time	Blood Sugar, per Cent.	Diet				Urine
		Protein	Fat	Carbohydrate	Total Calories	
8:00 a.m.	0.14*	..	..	..	...	Contains no sugar on this day
8:20 to 8:35	....	35	38	35	640	
9:36	0.16					
10:32	0.17					
11:32	0.14					
12 m. to 1z:30 p.m.	....	58	60	42	908	
1:39	0.17					
2:30	0.17					
3:33	0.17					
4:30	0.17					
5:15 to 5:35	....	41	50	41	801	
6:55	0.17					
8:30	0.15					

Table 20.—Hourly determinations of blood sugar in a case of diabetes mellitus. Patient on a diet containing a moderate amount of starch. There is a rise of the percentage of blood sugar after breakfast which is not exceeded throughout the day.

* Fasting.

able blood sugar level will be proportionately increased. When this optimum glucose percentage in the blood is reduced by dietary restrictions, the organism tends to respond by a hyperglycemia on the least provocation. It is under such circumstances that there occurs an increase in the glucose of the blood after the ingestion of protein and fat. Such reactions may go very far to explain the very wide variations in blood sugar often found in cases of diabetes.[8]

8. Mosenthal, H. O., and Lewis, D. S.: Bull. Johns Hopkins Hosp., 1917, **28**, 187.

It has been shown previously by von Moraczewski[9] that the blood sugar rises after exercise, and that, in spite of this hyperglycemia, the tolerance for sugar is greater after muscular effort than during rest, when the blood sugar is lower. This holds true, apparently, for the diabetic as well as for the normal individual. Tests of the concentration of the blood in these experiments showed that there was no diminution in the hydremia through sweating, which might have been responsible for an apparent increase in the percentage value of the blood sugar. Thus, it seems that the human organism is able to utilize glucose more effectively when the blood sugar is at a high level than at a low one. This is frequently observed clinically and brings up the much debated question whether it is wise to attempt to reduce the blood sugar in every case of diabetes mellitus to a normal level. From the facts given here it would appear that there are some arguments in favor of not carrying such an endeavor too far.

Summary of Table	Blood Sugar per Cent.						
	Fasting	After Breakfast		After Lunch		After Supper	
		Maximal	Minimal	Maximal	Minimal	Maximal	Minimal
9	0.18	0.18	0.17	0.17	0.13	0.17	0.11
10	0.45	0.45	0.45	0.45	0.45	0.45	0.45
11	0.23	0.23	0.23	0.23	0.23	0.23	0.19
12	0.33	0.33	0.33	0.33	0.32	....	0.28
13	0.18	0.18	0.18	0.19	0.18	0.18	0.18
14	0.17	0.17	0.17	0.18	0.18	0.18	0.18
15	0.12	0.19	0.16	0.20	0.16	0.16	0.14
16	0.15	0.19	0.15	0.19	0.11	0.17	0.15
17	0.14	0.16	0.16	0.18	0.16	0.16	0.16
18	0.13	0.16	0.13	0.14	0.08	0.18	0.15
19	0.16	0.25	0.23	0.23	0.22	0.26	0.22
20	0.14	0.17	0.14	0.17	0.17	0.17	0.15

Table 21.—Summary from preceding tables. Summary of the hourly determinations of blood sugar in cases of diabetes mellitus on a carbohydrate-free diet, or one containing a moderate amount of starch. If there is a rise of blood sugar in the course of the day, the maximal value reached one or two hours after breakfast is usually not exceeded to any marked degree after lunch or supper. There frequently is a diminution in the glycemia in the afternoon and evening.

9. Von Moraczewski, W.: Berl. klin. Wchnschr., 1915, **52,** 1038; ibid., Ztschr. f. biol. Chem., 1915, **71,** 268.

SUMMARY

The maximal percentage of blood sugar occurring in diabetic individuals on a carbohydrate-free diet, or one containing a moderate amount of starch, can be obtained by making the determinations one to two hours after breakfast. The glycemia may rise somewhat higher after lunch or supper, but never to any marked degree. On the other hand, the blood sugar may fall considerably in the afternoon and evening hours, leading to erroneous interpretations if taken at this time of day (Table 21).

In diabetic cases there is a tendency for the blood sugar to remain constant throughout the day while on a protein-fat diet, if the fasting blood sugar is high; on the other hand, if the fasting blood sugar is low, that is, if it has been reduced by previous dietetic treatment, there is an increase which may become very marked in the glycemia after carbohydrate-free food (Table 21). This leads to the conclusion that cases of diabetes mellitus, in raising their fasting or basal blood sugar percentage, are trying to adjust their carbohydrate metabolism for the more advantageous utilization of glucose. It may be desirable, therefore, not to attempt to reduce the blood sugar to a normal value in cases of diabetes mellitus.

Johns Hopkins Hospital.

STIMULATION OF THE RESPIRATION BY SODIUM CYANID AND ITS CLINICAL APPLICATION *

A. S. LOEVENHART, M.D., W. F. LORENZ, M.D.
H. G. MARTIN, M.D., AND J. Y. MALONE, M.D.
MADISON, WIS.

The stimulation of the respiration by hydrocyanic acid has been known ever since its physiologic action was first investigated. It was sought to utilize this extremely obvious stimulation of the respiration therapeutically, and we find articles published in the first half of the last century lauding its use as a respiratory stimulant.[1] The depressing action of hydrocyanic acid was also noted.[2] The only remnant of this once prominent remedy left in modern therapeutics is the use of hydrocyanic acid in certain cough mixtures.

Geppert[3] established that the action of hydrocyanic acid is essentially asphyxiation, since it acts by decreasing the oxygen absorbed by the tissues and also the carbon dioxid produced by them.

The attitude of modern pharmacologists on the therapeutic use of hydrocyanic acid may be gathered from the following:

Heinz[4] says that hydrocyanic acid is one of the strongest stimulants for the respiration known, but that its stimulating action cannot be used in practice because it is too poisonous.

Cushny[5] declares: "Prussic acid might be eliminated from therapeutics without loss."

Sollmann[6] says: "There seems to be no rational basis for the therapeutic use of cyanids."

Bastedo[7] makes virtually the same statement.

It is our opinion that the disrepute into which hydrocyanic acid has fallen is due to the following: (1) the fact that its action is fleeting, since it is apparently rapidly transformed into the nontoxic sulpho-

* Submitted for publication Aug. 21, 1917.

1. Ryan: Tr. Coll. Phys., 1828, **5,** 479.

2. Magendie, F.: Physiological and Chemical Researches on the Use of Prussic Acid, etc., 1820, New Haven; Granville, A. B.: Further Observations on the Internal Use of Hydrocyanic Acid (Prussic Acid), 1819, London; Coullon, J. J. A.: Considerations médicales sur l'acide prussique, 1808, Thésis Medicine, Paris.

3. Geppert, J.: Ztschr. f. klin. Med., 1889, **15,** 208, 307.

4. Heinz: Handbuch der Experimentellen Pathologie und Pharmakologie, Jena, 1906, 2, **1,** 588.

5. Cushny, A. R.: A Textbook of Pharmacology and Therapeutics. Philadelphia, Lea & Febiger, 1915, p. 453.

6. Sollmann, T.: A Manual of Pharmacology. Philadelphia, W. B. Saunders Company, 1917, p. 617.

7. Bastedo: Materia Medica; Pharmacology. Philadelphia, W. B. Saunders Company, 1913, p. 403.

cyanate; (2) the rate of absorption from the stomach is sufficiently uncertain so that either no effect follows its administration or too intense an effect is noted; (3) instability of all preparations of hydrocyanic acid; (4) the popular idea that the cyanids are so very poisonous.[8]

We determined to investigate the subject from the standpoint of modern intravenous therapeutics, substituting sodium cyanid for hydrocyanic acid. Sodium cyanid of fair purity is now on the market.[9] This substance is perfectly stable in the solid state if kept in tightly stoppered, well filled bottles. It is very soluble in water. Our solutions were always freshly prepared, the oldest used by us having been prepared forty-eight hours before administration. The sodium cyanid was dissolved in sterile physiologic salt solution.

We prefer sodium cyanid to potassium cyanid because of the depressing effect of potassium salts on the heart. The effect of the soluble cyanid is essentially the same as that of hydrocyanic acid.

We have studied the stimulating action of sodium cyanid on the respiration in animals and in man. A detailed statement of the work on animals will soon be published in the *Journal of Pharmacology and Experimental Therapeutics*. However, a brief statement of the experimental work which preceded the clinical application of the method is essential. The experiments were nearly all performed on dogs; only a few rabbits were used in the early part of the work. The effect of sodium cyanid on the depressed respiration was determined under the following conditions:[10] morphin poisoning, stoppage of respiration from

8. The popular view that the cyanids are among the most poisonous substances known seems to be due to the statement by Magendie that animals, if given hydrocyanic acid, die as quickly as though they had been hit by a cannon ball. While all will admit that fatal doses of hydrocyanic acid kill with great rapidity, the dose of the cyanids required to kill is far above that of many other substances. The fatal dose of hydrocyanic acid is usually placed at from 30 to 100 mg., and the fatal doses of sodium cyanid and potassium cyanid on an equimolecular basis are, respectively, from 50 to 167, and from 72 to 240 mg. Much greater quantities than this can be given in small divided doses over a longer period of time without deleterious effects, due to the rapid detoxification in the body.

9. The sodium cyanid which we used was manufactured by Kahlbaum and contained from 92 to 95 per cent. of sodium cyanid.

10. A drug may be clearly indicated to modify abnormal functioning due to one cause and may be entirely worthless in the same form of abnormal function due to another cause. For instance, in bradycardia due to excessive vagal tone, atropin is the only drug to be used to increase the pulse rate. However, if the bradycardia is due to heart block atropin will be of no avail. Again, digitalis is perhaps the first drug one would consider to reduce a rapid pulse rate. It is the drug of choice if the rapid pulse is due to decreased vagal tone, low blood pressure and cardiac dilatation, but it is worse than useless in simple febrile tachycardia. Any number of similar examples might be given, all of which indicate that in order to treat rationally a given abnormality of function we must know the cause of the abnormal function so far as we can analyze the condition.

deep chloroform and ether anesthesia, hemorrhage, and increased intracranial pressure. By far the greater part of the work was done on animals under increased intracranial pressure. Such a condition is met with clinically as a result of basilar fracture, intracranial hemorrhage, brain tumors, etc. In addition to determining the effect of sodium cyanid on the respiration under increased intracranial pressure, we studied the effect of the following drugs on the respiration under this condition for comparison with the cyanid; namely, caffein citrate, strychnin sulphate, atropin sulphate and lactic acid.

In the experiments on increased intracranial pressure, a cranial cannula was put in place and the pressure transmitted by Ringer's solution. Sixty-two experiments were performed under increased pressure. Our method of experimentation in the main was as follows:

The intracranial pressure was gradually increased to the point at which the respiration ceased. The degree of anemia of the respiratory center at which all activity ceases varies in different animals and must be determined in each experiment. Now, with this degree of anemia maintained, the drug whose effect on the respiration it was desired to study was injected intravenously, the dosage varying throughout the range of the probably useful amounts. The results of the experimental work may be summarized as follows:

1. Caffein citrate and atropin sulphate are useless in the treatment of respiratory depression due to increased intracranial pressure. It seemed that the death of the animal was hastened by the administration of either of these drugs in sufficient quantities to have any observable effect.

2. The action of lactic acid when administered under the conditions stated varies remarkably in different animals. In some dogs no effect whatever was noted, while in others it proved to be quite an efficient stimulus to the respiration. The stimulation lasted for quite a period of time, but in all cases the animal died from respiratory failure, and we do not consider lactic acid as a useful stimulant to the respiration under these conditions.

3. Strychnin sulphate administered to dogs with the respiration depressed by increased intracranial pressure caused a distinct stimulation of the respiration. The latent period of the stimulating action of strychnin averages twenty-seven seconds. The stimulation lasted over a considerable period of time; the longest period of stimulation being twenty-eight minutes, after a single dose. In many cases a peculiar type of group respirations was noted under strychnin.

4. The result of intravenous administration of sodium cyanid to dogs under increased intracranial pressure may be briefly indicated as follows:

(*a*) It causes stimulation of the respiration, when properly used, practically up to the time of the death, and is undoubtedly the strongest known stimulant to the respiration in this condition.

(*b*) The average latent period of its action is from six to nine seconds.

(*c*) The intensity and duration of the stimulation depends on the dose and rate of administration. As a result of a single injection within a few seconds, the average duration of stimulation is from ten to fifteen seconds. The longest period of stimulation following a single injection was one hour. If too much sodium cyanid is given within a given period of time, a brief period of stimulation followed by depression will be noted.

(*d*) By means of a slow continuous intravenous injection of sodium cyanid, a continuous stimulation of the respiration of almost any desired intensity may be obtained.[11] A constant stimulation of the respiration was maintained for a period of two hours by a continuous slow intravenous injection of hundredth-normal sodium cyanid, with the intracranial pressure maintained at a level which had previously repeatedly been demonstrated to paralyze the respiration in the same animal. In these slow continuous injections, every slight change in the rate of injection causes its corresponding change in the respiratory movements.

(*e*) The margin of safety in the intravenous administration of sodium cyanid in dogs may be gathered from the following data:

(1) The amount of sodium cyanid required to give a decided stimulation in a single rapid injection is approximately 0.1 c.c. per kilogram.

(2) The amount of sodium cyanid required in a continuous slow injection to maintain a satisfactory stimulation under increased intracranial pressure, is 1 c.c. of a hundredth-normal solution in one and a half to three and a half minutes for a dog of about 10 kg.

(3) It is well known that sodium cyanid is quickly transformed in the body to a nontoxic substance, supposedly the sulphocyanate. We have endeavored to determine the rate at which it is detoxified in the organism by determining the maximum rate at which it can be injected intravenously without producing any symptoms whatever. These observations were made on dogs which were not subjected to increased intracranial pressure, and the maximum rate at which a hundredth-normal solution of sodium cyanid may be injected without producing any symptoms whatever was found to be 1 c.c. per one and one-half minutes. It would seem, therefore, that the animal under

11. The action of the cyanid in these experiments reminds one of the stimulation of the respiration by carbon dioxid.

increased intracranial pressure is somewhat more sensitive to sodium cyanid than the normal anesthetized animal.

(4) The fatal dose of hundredth-normal sodium cyanid rapidly injected from thirteen to twenty-five seconds intravenously is from 2.63 to 3.3 c.c. per kilogram of body weight. The smaller dose killed a dog in sixty-three minutes while the larger dose killed in twelve minutes.

Since 2 c.c. hundredth-normal sodium cyanid injected within three seconds caused stimulation even in our largest dogs, the therapeutic dose per kilogram may be placed at 0.1 c.c. per kilogram. Hence, twenty times the therapeutic dose when administered rapidly kills in about one hour.[12]

(*f*) As a result of our early experiences with sodium cyanid, showing how ephemeral is the stimulating effect of a single dose, we sought by means of administering sodium cyanid and strychnin sulphate in sequence to obtain a greater and more lasting stimulation of the respiration than could be obtained with either drug alone. Our work indicates, in the dog at least, under conditions of increased intracranial pressure that this is true. The later work on the slow continuous injections of sodium cyanid, however, causes us to attach somewhat less importance to the sodium cyanid-strychnin sequence. It may, however, prove to be a very useful method clinically.

(*g*) Under the condition of this work and the dosage here used we have found that sodium cyanid has remarkably little effect on the circulation. Thus the pulse rate is, in general, but slightly decreased, and the blood pressure but little altered.

CLINICAL WORK

Having convinced ourselves through our mammalian work that the margin of safety in the intravenous administration of sodium cyanid is ample for human therapy, it was determined, as opportunity presented itself, to study the therapeutic effect of sodium cyanid in suitable human cases such as the following: (1) cases of increased intracranial pressure from any cause which show depression of the respiration. It should be stated that we did not propose to use sodium cyanid when an operation for decompression was indicated, but simply to stimulate the respiration by sodium cyanid in the interim between the failure of respiration and the time when operative measures could be instituted; (2) failure of the respiration under chloroform and ether anesthesia; (3) in bedridden cases in advanced paresis when

12. Since the fatal injections were given over a longer period of time it may be that the exact margin of safety may be less. Further work must determine this.

a hypostatic pneumonia was in the process of developing. In this instance it was hoped that the respiratory exercise induced by the sodium cyanid would improve the pulmonary condition and at least delay the fatal outcome.

Accordingly, we made fifteen intravenous injections in ten cases.

METHODS

Our first work indicated clearly that a fiftieth-normal solution of sodium cyanid is preferable to the hundredth-normal solution in human therapy. A fiftieth-normal solution of sodium cyanid should contain 0.98 mg. per cubic centimeter. In our work, however, what we have called a fiftieth-normal solution was actually made up by dissolving 1 mg. per cubic centimeter in physiologic salt solution. The sodium cyanid was dissolved in sterile 0.9 per cent. salt solution and was handled aseptically. Since solid sodium cyanid is free from bacteria, it is unnecessary to sterilize after dissolving the sodium cyanid. In fact, such a sterilization would change the concentration of the solution to such an extent that an analysis would have to be made to determine its strength. It is, therefore, not permissible to sterilize the solution after dissolving the cyanid.

TECHNIC

The injections were made with 20 c.c. record syringes, or from 50 c.c. burets. The injections were all made in the median basilic vein. In addition to the intravenous injections, several intramuscular injections were made, and in one case, through faulty technic, quite an amount of the fiftieth-normal sodium cyanid was injected into the perivascular tissue. In no case was there any sign of inflammation or local irritation.

The rate of administration is all important, and it is necessary to time the injection exactly. This point will be brought out later.

The respiration was recorded by means of a tambour. One or two large, thin-walled volley-ball bladders were placed over the chest and abdomen and a canvas bandage fixed about the patient and the bladders. The bladders were connected by a Y tube and then with the tambour by means of a rubber tube. In the tables which follow we have recorded the respiratory rate before and after the administration of the drug, and also the total linear excursion of the lever of the tambour in centimeters in twenty seconds. This latter figure would be an exact measure of the lung ventilation were our method of recording the respiration perfect. This is not the case, however, but we regard the figure obtained as probably roughly proportional to the lung ventilation, or at least as near an approximation to it as we were able to obtain.

A Jaquet time-marker recorded the time in seconds, and a marking pen was used to indicate any procedure. The pulse was taken at the wrist throughout at intervals. Systolic and diastolic blood pressure determinations were made in one case, but no change in the blood pressure was noted.

CASES IN WHICH TREATMENT WAS ADMINISTERED

Case 1.—H. H., man, aged 39, weight 160 pounds. General state of nutrition good. Heart enlarged, apex beat in sixth interspace beyond nipple line. Loud blowing, systolic murmur, with maximum intensity at second interspace on right side and transmitted into vessels of the neck and the left axillary

space. Murmur also heard at the apex. Thickening of radial, brachial and temporal arteries.

Diagnosis.—Dementia paralytica.

This patient received a total of 26 c.c. of fiftieth-normal sodium cyanid or 26 mg. of sodium cyanid within a period of sixteen minutes. The administration of 1 c.c. in thirty seconds was the slowest rate of injection that caused a stimulation of the respiration. Injection of 1 c.c. per thirty, twenty, fifteen, twelve, and ten seconds caused increasing responses. During the period in which he received 1 c.c. in fifteen seconds the rate remained unchanged, but the amplitude of the respiration doubled. A series of injections of 1 c.c. at intervals of one-half minute each called forth a beautiful response, the amplitude again being increased without any change in the rate. The duration of the stimulation following a single injection was approximately twenty seconds. It was observable in this case that during marked stimulation the accessory respiratory muscles of the neck were used. At the end of the injection some flushing of the face was noted.

CASE 2.—E. L. E., man, aged 48, weight 90 pounds.

Diagnosis.—Dementia paralytica.

The patient was bed ridden, semicomatose, and becoming progressively weaker. It was impossible to arouse him; the eyes were constantly closed. The patient was much emaciated.

TABLE 1.—CASE 2, TREATMENT 1

May 18, 1917

No.	Procedure N/50 NaCN, C.c.	Time	Respiration per 20 Seconds				Remarks
			Before		After		
			Rate	Vent.	Rate	Vent.	
1	2	2:09	6.0	6.0	6.0	8.0	Pulse 80 per min.; 2 c.c. administered in 3 sec.
2	3	2:10	6.0	5.5	6.5	13.5	Pulse 80-90-80. 3 c.c. administered in 6 sec.
3	3	2:13	6.5	5.3	7.5	16.0	Apnea of 15 sec. followed stimulation. Figure 1, A.; 3 c.c. administered in 10 sec.; pulse 84
4	5	2:16	6.0	5.3	8.0	21.9	5 c.c. administered in 7 sec.; apnea of 32 sec. followed stimulation; pulse during apnea 86; pulse when respiration was resumed 78, Figure 1, b
5	7	2:20	6.0	5.8	10.0	26.4	Pulse 88; apnea of 40 sec. followed stmulation, during which pulse was 104; 7 c.c. were injected in 11 sec.; after stimulation passed, respiratory rate was 5 in 20 sec.; linear measure 4.8 cm.; Figure 1, C
6	0.5 mg.	2:27	6.0	6.1	5.0	5.0	Pulse 72
	strychnin sulphate	2:28	....	....	5.5	6.7	Pulse 66
		2:33	....	....	6.5	6.0	Pulse 70

Patient 2 received 20 c.c. fiftieth-normal sodium cyanid or 20 mg. of sodium cyanid in a period of thirty-four minutes. The apnea following each rapid injection of sodium cyanid is roughly proportional to the intensity of the stimulation of the respiration and this again is almost proportional to the dose of sodium cyanid and the rate of injection. We therefore regard the respiratory pause following the stimulation as a true apnea. This patient also received 0.5 mg. of strychnin sulphate intravenously in a period of thirty-four minutes. The strychnin did not stimulate the respiration. There was a latent period of reaction to sodium cyanid of twenty-one seconds. Increase in pulse rate 30 per cent.

CASE 2.—*Treatment 2.*—June 11, 1917. As the results of this treatment were similar to those in the first they are not tabulated. The patient received 82 c.c. fiftieth-normal sodium cyanid or 82 mg. of sodium cyanid in a period of forty-five minutes injected slowly. The increase in the pulse rate was 23 per cent., and the latent period of reaction to the sodium cyanid thirteen seconds.

TABLE 2.—CASE 2, TREATMENT 3

June 12, 1917 (Buret injection)

No.	Procedure N/50 NaCN, C.c.	Time	Respiration				Remarks
			Before		After		
			Rate	Vent.	Rate	Vent.	
1	19 slowly	8:12	5	5.9	5	7.4	1 c.c. in 15 sec.
					7	13.4	1 c.c. in 10 sec.
					6	7.5	1 c.c. in 40 sec.
					9	24.7	1 c.c. in 10-20 sec.; total 19 c.c. in 6 min.
					6	5.0	After cessation of injection
3	15 slowly	8:22½	5	4.0	6	11.5	2 c.c. in 20 sec.
					7	11.7	1 c.c. in 15 to 20 sec.
					7	6.8	1 c.c. in 25 sec.
					9	22.2	1 c.c. in 20 sec. Total 15 c.c. in 5 min. 2 c.c. NaCN first injected to remove blood in needle. Patient received 34 mg. NaCN or 34 c.c. N/50 NaCN in 20 min. (Demonstrated before the Dane County, Wis., Medical Society)

CASE 2.—*Treatment 4.*—June 15, 1917. Two c.c. of fiftieth-normal sodium cyanid intravenously produced the same stimulating effect as in the first treatment, while 10 c.c. intramuscularly showed only a slight stimulating effect. The patient received 40 c.c. fiftieth-normal sodium cyanid or 40 mg. sodium cyanid in a period of forty minutes. The latent period of reaction to the sodium cyanid was eighteen seconds.

CASE 3.—C. L. E., man, aged 36, weight 135 pounds.

Diagnosis.—Dementia paralytica.

The patient was bed ridden, unable to speak, and has convulsions, with brief intervals of relaxation between seizures.

TABLE 3.—CASE 3

June 15, 1917.

No.	Procedure N/50 NaCN, C.c.	Time	Respiration				Remarks
			Before		After		
			Rate	Vent.	Rate	Vent.	
3	2	2:18	7	4.9	8.0	6.4	1 c.c. in 10 sec.
5	10 slowly	2:20¼	7	5.8	8.0	7.9	
6	5	2:25	7	6.8	8.0	10.4	Pulse 96
9	2	2:40	7	5.8	7.5	5.9	
10	9 slowly	2:41	8	6.0	9.0	9.0	1 c.c. in 14 sec.
					12.0	12.4	Pulse 96. Total, 9 c.c. in 2 min.
14	18	2:56	8	5.9	8.0	11.4	The 18 c.c. were given 1 c.c. at a time. For effects note Figure 2
					8.0	7.8	
					10.0	9.1	
					11.0	9.8	Cough
					9.0	10.4	
26	.....	3:06	....	....	10.0	10.2	Face flushed; total 18 c.c. in 10½ min.
29	1	3:09¾	9	6.2	10.0	9.9	
30	1	3:11	8	5.2	10.0	10.8	
31	5 slowly	3:13	8	5.7	9.0	9.0	1 c.c. in 19 sec.; total 5 c.c. in 1½ min.: pulse strong, 112
					10.0	10.5	
42	4.5 in muscle	3:46	7	6.9	7.0	7.9	
43	5 in muscle	3:48	8	6.7	8.0	8.2	Injection lasted ¼ min.: massaged point of injection
45	10 in muscle	3:55	8	6.0	4.0	8.4	
					10.0	9.85	Pulse 104; at 4:14 pulse was 96

Less muscle twitching when drug is being given. Responds to call of name. No convulsions precipitated by administration of drug. Had many convulsive attacks in the previous few days. Increase in pulse rate 16 per cent. This patient received 72.5 c.c. fiftieth-normal sodium cyanid or 72.5 mg. sodium cyanid in one hour and forty minutes. Latent period of respiratory stimulation 11 seconds.

CASE 4.—G. E. F., man, aged 26, weight 140 pounds. Heart normal in size. Loud systolic murmur at apex transmitted to the left; audible along sternum and at base. Blood pressure: systolic 90, diastolic 50.

Diagnosis.—Dementia praecox, catatonic form.

The patient was always very quiet, sat by himself, made no effort to speak to any one and could not be induced to answer questions. Had become emaciated.

TABLE 4.—CASE 4

June 15, 1917.

No.	Procedure N/50 NaCN, C.c.	Time	Respiration				Remarks
			Before		After		
			Rate	Vent.	Rate	Vent.	
3	2	4:32¾	4.0	3.8	5.0	5.7	
4-7	8	4:33¼	....	....	4.0	4.9	Total 8 c.c. in 2¾ min. (2 c.c. at a time); pulse 52
8	2	4:37	4.0	4.9	5.0	6.4	
9	8	4:38¼	3.5	4.0	4.5	7.8	Total 8 c.c. in 3½ min. (5 c.c., 1 c.c., and 2 c.c.)
14	5	4:46¾	3.5	4.2	4.0	8.1	
15	2	4:49¼					
16	2	4:51¼	4.0	3.8	4.0	5.45	
17	12 slowly	4:52½	4.0	3.65	4.0	10.7	1 c.c. in 9 sec.
					6.0	8.85	1 c.c. in 15 to 20 sec.; respirations very regular; pulse 128
19	.....	4:58½	....	....	....	....	Pulse 100 at 4:58½; 88 at 5:00¾, and 86 at 5:02
22	2	5:10	4.0	4.15	4.0	6.1	Pulse, 72 before injection; 84 after injection
23	2	5:12	4.0	4.9	4.0	6.5	
24	2	5:13¾	4.0	3.8	4.0	7.0	
25	6 slowly	5:15¼	4.0	4.15	4.0	8.4	1 c.c. in 16 sec.; respiration very regular; pulse 100
		5:17	....	....	5.0	9.45	Pulse 100; drops to 88.
26	3	5:21¼	4.5	3.5	4.0	7.85	Pulse 86
30	2	5:27½	3.5	3.85	4.0	6.25	Pulse 84; patient somewhat restless
32	4 slowly	5:34½	2.5	2.6	5.0	8.4	Pulse 84; 1 c.c. per 10 sec. Latent period for slow injections averages 15 sec.; patient in good condition after treatment and much better than before; patient received 64 mg. NaCN, or 64 c.c. N/50 NaCN in 1 hr. 15 min.; increase in pulse rate, 146 per cent.; latent period averages 23 sec.

CASE 5.—W. H. Y., man, aged 45, weight 120 pounds; treated June 16, 1917.

Diagnosis.—Dementia paralytica.

After subcutaneous injections the stimulation was negligible, while only after large quantities intramuscularly was there any stimulation noted. Intravenous injections produced stimulating effects as in other cases. Increase in pulse rate 26 per cent. Latent period twenty-three seconds.

CASE 6.—J. H., man, aged 21, weight 125 pounds.

Diagnosis.—Dementia praecox.

The patient was always extremely sluggish, made no effort to talk to anyone. Was up and about every day. State of nutrition poor.

TABLE 5.—CASE 6

June 19, 1917.

No.	Procedure N/50 NaCN, C.c.	Time	Respiration				Remarks
			Before		After		
			Rate	Vent.	Rate	Vent.	
5	2	9:22¾	5	5.6	5	5.9	Pulse 66
6	2	9:24	5	5.4	5	6.5	
7	2	9:25	5	5.1	5	5.7	
8	..	9:26½	5	5.7	5	8.1	
9	5	9:29½	5	4.8	5	8.7	Pulse 69
12	20 slowly	9:32½	5	4.2	5	7.8	1 c.c. in 10 to 14 sec.
					6	11.7	Pulse 99; total 20 c.c. in 3½ min.; slight flushing of face; no cyanosis. See Figure 3
15	1	9:46¼	5	4.8	5	6.1	
16	2	9:47¼	5	6.5	5	7.4	
18	1	9:51½	5	4.7	5	5.6	
19	15 slowly	9:52¾	5	4.8	4	7.8	1 c.c. in 10 to 14 sec.; face flushed
					5	7.9	1 c.c. in 10 to 20 sec; pulse 105, strong
					5	10.5	1 c.c. in 10 sec.; total 15 c.c. in 5 min.; skin moist
21	1	10:00¼	6	3.5	5	5.1	
22	1	10:01	5	5.1	yawn		
25	2	10:05	4	2.8	4	5.6	Pulse 90
26	2	10.06	4	5.6	3	5.8	

Results in the remainder of the treatment were similar to those recorded in the table. Patient received in all 111 c.c. fiftieth-normal sodium cyanid in one hour and fifteen minutes. Fifty-nine per cent. increase in pulse rate. Latent period twenty-one seconds.

CASE 7.—D. G. E., man, aged 25, weight 155 pounds.

Diagnosis.—Dementia praecox.

Patient received 157 c.c. fiftieth-normal sodium cyanid, or 157 mg. sodium cyanid in a period of one hour and fifty-eight minutes; patient in very good condition after treatment; no vertigo; pulse rose from 54 to a maximum of 87; latent period of stimulation of respiration twenty-two seconds.

CASE 8.—L. C., man, aged 39, weight 100 pounds.

Diagnosis.—Dementia paralytica.

For the previous eight months he had been confined to his bed.

TABLE 6.—CASE 8

June 21, 1917.

No.	Procedure N/50 NaCN, C.c.	Time	Respiration				Remarks
			Before		After		
			Rate	Vent.	Rate	Vent.	
3	2	10:20¾	6	10.2	5	7.8	
4	2	10:21	5	7.8	7	11.1	
5	1	10:22	....	....	6	9.2	
6	5 slowly	10:22¼	6	9.2	7	11.9	
8	5 slowly	10:25	6	7.4	7	12.5	
10	27 buret	10:31	6	7.6	8	17.5	Pulse 108; total 27 c.c. in 9 min.
					7	10.8	1 c.c. in 27 sec.
					7	14.5	1 c.c. in 14 sec.
					9	17.4	
14	13 slowly	10:41	7	8.5	7	13.6	Total 13 c.c. in 6¼ min.; pulse 108 at 10:41 a. m.
					8	16.7	Pulse 68 at 10:55 a. m.
26	2	11:06¼	7	11.3	7	16.9	
27	2	11:06¾	7	10.9	7	15.2	
28	16 slowly	11:06½	7	15.2	8	17.7	1 c.c. in 22 sec. Total 16 c.c. in 5½ min.; pulse 100 at 11:15 a. m.
33	2	11:19½	7	10.4	7	16.7	Pallor
34	2	11:21¼	6	13.0	8	15.5	
35	6 slowly	11:22½	7	13.7	8	18.7	1 c.c. in 18 sec.; total 6 c.c. in 2½ min.; hiccough; pallor
39	2	11:35	8	19.2	8	22.0	Pallor. Note Figure 4

Patient in good condition after treatment. Patient received 93 c.c. fiftieth-normal sodium cyanid, or 93 mg. in a period of one hour and twenty-two minutes. Latent period twenty seconds.

CASE 9.—N. J., man, aged 60, weight 140 pounds.

Diagnosis.—Dementia paralytica.

Patient had been confined to bed for eighteen months.

TABLE 7.—CASE 9, TREATMENT 1

June 21, 1917. Buret injection.

No.	Procedure N/50 NaCN, C.c.	Time	Respiration				Remarks
			Before		After		
			Rate	Vent.	Rate	Vent.	
9	5	2:05¾	11	8.4	11	11.6	
11	1	2:06¼	....	....	....	....	1 c.c. in 8 sec.; no effect on respiration
12	2	2:07¼	12	8.4	12	12.7	
13	2	2:08½	11	6.4	11	12.9	2 c.c. in 10 sec.
14	29.5 slowly	2:10	11	6.9	12	10.5	Pulse 94; 1 c.c. in 18 to 22 sec.
					11	11.2	Pulse 102; face flushed
		2:20	....	....	12	16.8	Pulse 100; 1 c.c. in 25 sec.; total of 29.5 c.c. in 10½ min.
19	15 slowly	2:23	11	10.8	11	18.9	1 c.c. in 15 sec.; face flushed. Note Figure 5
					12	12.1	1 c.c. in 12 to 40 sec.
					13	19.3	1 c.c. in 25 sec.
					12	20.7	1 c.c. in 28 sec.; pulse 100; total, 15 c.c. in 10 min.
34	10 intramuscularly	2:57¾	13	12	13	11.7	Apparently no response
					13	12.5	

Patient received 65 c.c. fiftieth-normal sodium cyanid or 65 mg. sodium cyanid in a period of one hour. Increase in pulse rate 8 per cent.; latent period twenty seconds.

CASE 10.—T. Z., man, aged 21, weight 160 pounds. Admitted to the hospital June 25, 1917, and had not spoken since admission, and therefore no history could be obtained. Immediately following the injection he talked freely and gave a history which was later verified. His mental condition was still improving.

Diagnosis.—Dementia praecox.

TABLE 8.—Case 10

June 27, 1917. Buret injection.

No.	Procedure N/50 NaCN, C.c.	Time	Respiration				Remarks
			Before		After		
			Rate	Vent.	Rate	Vent.	
7	1	10:06¼	6	5.3			
8	1	10:06½	....	....	7	7.1	
9	1	10:07	....	....	6	5.8	
10	2	10:07½	6	5.8	7	7.8	
11	3	10:09	7	6.8	7	7.5	Pulse 74
12	5	10:10	7	6.8	8	12.1	
13	5	10:11¾	7	5.8	7	10.8	
14	2	10:13¾	7	7.0	7	8.7	Response to 2 c.c., while there was little response to 3 c.c. before the 5 c.c. in Precedure 12
15	2	10:16½	7	5.6	7	7.8	Total 22 c.c. during this period
18	2	10:20¾	7	7.3	7	7.5	
19	5	10:21½	6	5.4	5	12.7	Apnea of 13 sec. followed this stimulation
20	1	10:33½	6	4.7	7	6.5	Response here to 1 c.c. following 5 c.c., while before this injection there was no response to 2 c.c.
21	2	10:24¾	7	6.1	7	7.0	
22	3	10:26	6	5.4	7	8.1	
23	3	10:27	6	5.5	6	8.0	Total 16 c.c. in 6¾ min.
24	20 slowly	10:28	6	5.9	6	9.3	1 c.c. in 15 sec.
					6	7.7	1 c.c. in 20 sec.
					7	10.7	1 c.c. in 11 sec.; pulse 106; face flushed; total 20 c.c. in 4½ min.
		10:35	....	....	8	7.6	Pulse 100
29	1	10:39½	7	5.7	6	6.0	
30	2	10:40¾	6	6.0	7	9.7	
31	2	10:42¼	7	6.5	7	10.0	Slight nausea (had 63 c.c. up to this time)
32	5	10:47¼	6	6.8	7	8.3	1 c.c. in 8 sec. (5 c.c. in 1½ min.)
34	2	10:49	7	5.6	7	8.3	2 c.c. in 5 sec.
35	2	10:50	7	5.9	7	8.5	2 c.c. in 4 sec.
36	2	10:51¼	7	5.7	7	8.4	2 c.c. in 11 sec.
37	2	10:55	6	5.0	7	7.8	2 c.c. in 19 sec.
38	1	10:55¼	7	5.8	7	6.8	1 c.c. in 4 sec.
41	1	10:57	6	5.1	7	7.4	

TABLE 8.—CASE 10—(*Continued*)

No.	Procedure N/50 NaCN, C.c.	Time	Respiration				Remarks
			Before		After		
			Rate	Vent.	Rate	Vent.	
42	3	10:58¼	6	5.4	6	11.9	3 c.c. in 5 sec.
43	3	11:00	6	5.0	6	10.8	3 c.c. in 10 sec.
44	3	11:02	6	5.9	7	10.0	3 c.c. in 16 sec.
45	3	11:03½	6	6.2	6	9.0	3 c.c. in 15 sec.
46	3	11:06	6	5.7	7	8.8	3 c.c. in 18 sec.
47	9	11:08½ 11:10½	....	....	8	9.5	1 c.c. in 12 to 16 sec.; total 9 c.c. in 2 min.; pulse 104; nausea; vomiting movements; pallor; pulse of good character
50	.....	11:15½	....	....	7	6.2	Pulse 70. Patient conversed all through latter part of injection. It was the first time he had made any sort of statement since his admittance to the hospital.

Patient received 102 c.c. fiftieth-normal sodium cyanid, or 102 mg. in a period of one hour and four minutes. He said he felt much better after the treatment. Increase in pulse rate 32 per cent.; latent period twenty-two seconds.

DISCUSSION OF RESULTS

The protocols, together with the tracings, show clearly that sodium cyanid is a reliable stimulant to the respiration in every case in which we have administered it. It should be noted that the graphic records of the respiration in our experiments do not show accurately the lung ventilation. Thus, with a change in the type of respiration the bladder or bladders might less perfectly record the respiratory movements. Frequently, following the administration of sodium cyanid, inspection of the chest clearly showed an enormous stimulation of the respiration, whereas the record shows but relatively slight stimulation. Throughout, we may say that the records rather minimize the degree of respiratory stimulation.

The therapeutic use of sodium cyanid in these cases has fully confirmed the results of the animal experiments, in that we have never had experience with any drug whose administration calls forth so exact a response in functional activity as is to be noted under the cyanid.

The exactness of the control of the respiration under sodium cyanid is well illustrated in Cases 2 and 3. Records of the cyanid injections in these cases are shown in Figures 1 and 2. In Case 2, Treatment 1, as will be seen from the table, the stimulation of the respiration, both as to amplitude and rate, on rapid injection, is roughly proportional to the dosage. In other cases the amplitude is markedly increased with

little or no change in the rate. Figure 1 illustrates the type of respiratory stimulation which it would be most desirable to obtain in the resuscitation of drowning individuals. The great respiratory movements as shown here following rapid injection of 5 c.c. fiftieth-normal sodium cyanid would be invaluable in expelling water from the lungs. The respiratory pause shown in the record is apparently physiologic following the very active respiration and occasions no alarm.

Figure 2 shows the remarkable control of the respiration under cyanid possibly even more strikingly. The series of "beads" in the record, each representing a period of respiratory stimulation, could be produced at will.

In regard to the margin of safety in the intravenous administration of sodium cyanid, we may say that in the fifteen therapeutic injections which we have made we have never experienced any alarming symptoms whatever either during the time of injection or at any time fol-

A B C

Fig. 1 (Case 2).—Tracing illustrates the exactness of the control of the respiration under sodium cyanid; *A*, apnea of fifteen seconds followed stimulation; *B*, apnea of thirty-two seconds followed stimulation; *C*, apnea of forty seconds followed stimulation.

lowing it. On the other hand, we have seen in addition to the stimulation of the respiration observed during and immediately following the administration of the drug, a marked improvement in the general condition in many of these cases. Thus, Case 2, Treatment 2, on June 11, was expected to end fatally during the early afternoon. We were requested to administer the drug immediately as the respirations were extremely shallow. Before the injection the temperature was 102 F., the pulse was 88, and the respirations 22. The injection was followed by a marked improvement in the general condition of the patient, and the following morning his temperature was 98.8 F., pulse 72 and respiration 20. Each of the four injections was followed by very obvious improvement in the general condition of the patient.

The average latent period between the injection of the sodium cyanid and stimulation of the respiration in man was twenty seconds. It is of interest to note that the latent period for any given case was constant on a single day, but varied on different days.

The duration of stimulation from a single injection is almost proportional to the dosage and the rate of administration. The duration of stimulation, however, following a single rapid injection of sodium cyanid rarely exceeds thirty seconds.

The dosage required to give an outspoken stimulation of the respiration in man on rapid injection may be placed at from 3 to 5 c.c. of fiftieth-normal sodium cyanid.

A single rapid initial injection of 1 or 2 c.c. of fiftieth-normal sodium cyanid which fails to elicit a stimulation of the respiration will often cause a perfectly obvious stimulation when given a certain period of time following the injection of larger amounts administered either slowly or rapidly.

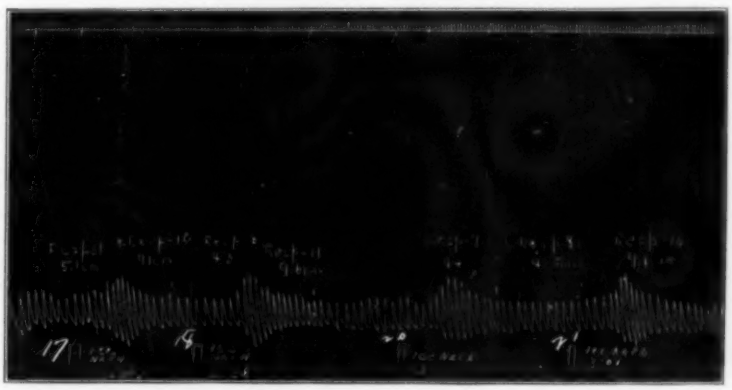


Fig. 2 (Case 3).—Illustrating the effect on the respiration of sodium cyanid given 1 c.c. at a time.

Our work throughout has confirmed the view that sodium cyanid is quickly transformed in the body to a nontoxic product. It is difficult to give the rate of detoxification in the body, but it would seem that the human body can detoxify sodium cyanid when injected intravenously at the rate of 1 c.c. per thirty or forty seconds, because when injected at this rate over a considerable period of time the drug produces no effect whatever. This offers the simplest explanation of the fact that doses which were insufficient to stimulate the respiration originally, may be efficacious when given a short time after other larger injections. It is also possible that a previous injection may increase the irritability of the respiratory center toward cyanid, but we are inclined to believe that this is not the true explanation.

Slow, continuous injections can be made by means of a syringe, although we obtained our most satisfactory results using the buret for such injections.

The effect of intravenous injections of sodium cyanid on the circulation which we have noted are as follows:

(*a*) Pulse rate. We have noted that in most of our injections there is a tendency to an increase in pulse rate. In some cases it was rather striking. In Case 4, Injection 1, after the injection of 37 c.c. of sodium cyanid, the pulse rate rose suddenly from 52 to 128. After a very short time the pulse rate dropped to 84. This is the most extreme case of increase in pulse rate which we noted. In other cases, the increase in pulse rate was much less, averaging 30 per cent.

(*b*) Blood Pressure. The blood pressure was taken by the auscultatory method in only one of our cases (Case 2, Injection 2). The variation of the blood pressure was well within the limit of error.

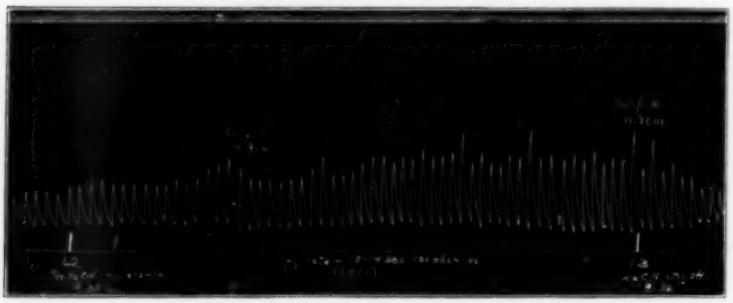


Fig. 3 (Case 6).—Showing the effect of constant stimulation during the slow continuous injection of 20 c.c. fiftieth-normal sodium cyanid.

(*c*) In certain of our cases in which there was a marked pallor of the skin before injection, we noted a general cutaneous hyperemia, in some instances with sweating. In other cases, merely a flushing of the face was noted, and in still other cases a pallor developed during injection which may have been associated with a tendency to nausea.

In Case 1, in which there was a serious heart lesion, no disagreeable symptoms of any kind were noted.

Vomiting center: In no case was actual vomiting produced by the injection of sodium cyanid. One patient, Case 7, stated that he felt sick after a slow, continuous injection. Another patient, Case 10, after an injection of 102 c.c. was nauseated, retching movements occurring. At this time there was a pallor of the face. The pulse was of good character.

Evidences of stimulation of the cerebrum as a whole, especially the psychic centers, was obtained in a number of cases. Thus, several patients, who had had their eyes closed for a long time, opened their eyes and looked about. In two instances they yawned quite naturally

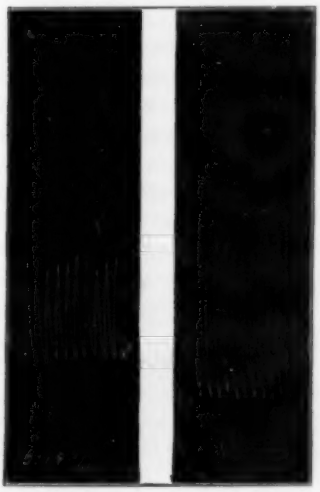


Fig. 4 (Case 8).—Effect of sodium cyanid on the respiration; *A*, normal tracing; *B*, shows stimulation eleven minutes after the injection of 6 c.c. fiftieth-normal sodium cyanid was completed.

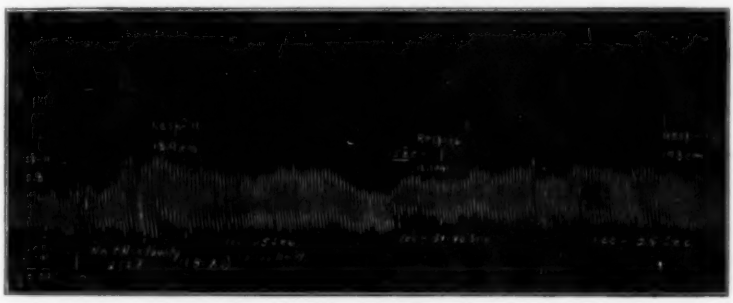


Fig. 5 (Case 9).—Illustrating stimulation of the respiration during an injection of sodium cyanid in which the rate of injection was varied.

as though they were awakening from a long sleep. The most interesting instance of psychic stimulation was observed in Case 10. This patient, who had dementia praecox, entered the hospital June 27, 1917, and up to the time of the injection had not spoken a word, so that no history was obtainable except from the meager statements on his commitment papers. After receiving an injection of 102 c.c. of fiftieth-normal sodium cyanid within a period of sixty-four minutes, the patient conversed, answered questions and attempted to explain his prolonged silence. His history was then obtained for the first time. We have, on the other hand, seen no evidences of motor stimulation. Case 3 clearly indicates the absence of motor stimulation. This man had been having one clonic convulsion after another for days, with occasional periods of rest. During the injection, and for some time following it, the convulsions did not occur and the muscular twitching was much less marked. In this case the cyanid seemed rather to depress than to stimulate the motor cortex.

Attention has already been called to the fact that subcutaneous, perivascular, or intramuscular injection of fiftieth-normal sodium cyanid in man does not cause any local inflammatory reaction. Therefore, from this point of view, the drug could be injected intramuscularly, but the dosage is not easy to determine when so administered and the delay in the therapeutic effect makes it impossible to gauge the dose nicely. For the present, therefore, we do not recommend intramuscular administration of the cyanid.

SUMMARY

The results of extensive animal experimentation, briefly summarized in the early part of this paper, necessitated a clinical investigation of the use of sodium cyanid as a respiratory stimulant. Our clinical results may be briefly summarized as follows:

1. We have treated ten patients with intravenous injections of fiftieth-normal sodium cyanid solution (0.1 per cent.). The treatment was repeated in some cases so that in all, fifteen treatments were given. In every case we have obtained a marked stimulation of the respiration on the average within twenty seconds after starting the injection. The stimulation could be accurately controlled by the rate of injection. The duration of the stimulation following a single injection depends on the dose and rate of injection. It rarely exceeds thirty seconds. The dosage required to produce therapeutic effects in man vary in different cases and according to the condition. Thus, in the case of resuscitation from drowning, it may be desirable to give an adult an injection of 5 c.c. of fiftieth-normal sodium cyanid within a period of ten seconds. This will give very large respiratory movements and should expel water from the lungs.

2. In other cases showing great depression of the respiration, when it is desired to produce a milder and more continuous form of stimulation of the respiration, it is desirable to give a slow, continuous injection of fiftieth-normal sodium cyanid intravenously at a rate varying from 1 c.c. in thirty seconds to 1 c.c. in fifteen seconds, depending on the degree of stimulation and the condition of the patient. Any competent observer watching the injection will have no difficulty in deciding the proper rate for a given case.

3. The injection should either be slowed or temporarily stopped on the appearance of any of the following symptoms: (1) marked pallor; (2) signs of nausea; (3) marked increase in the pulse rate; (4) depression of the respiration following too rapid injection or too large a dose, and (5) any other evident ontoward symptom should be the signal for stopping the injection.

4. The factor of safety in the intravenous administration of fiftieth-normal sodium cyanid is sufficiently large for clinical purposes.

5. It is our opinion that the intravenous injection of sodium cyanid may prove to be useful in the following conditions: (1) depression of the respiration resulting from increased intracranial pressure however produced, until the condition can be relieved by decompression; (2) resuscitation from drowning; (3) embarrassment of the respiration under any form of anesthesia, and (4) other forms of respiratory depression, when it may be given in addition to artificial respiration. Opportunity has not presented itself for us to study the effect of cyanid in all of these conditions.

6. The effects of sodium cyanid injections on the circulation are not such as would detract from its clinical use.

7. No disagreeable symptoms whatever developed as a result of the treatment in our clinical cases, and the condition of many of the patients was obviously improved. In addition to the stimulation of the respiration, there is evidence of stimulation of other parts of the cerebrum, especially the psychic functions.

8. It would seem superfluous to advise caution in the use of this drug. We believe, however, that the method is a perfectly safe one in the hands of a cautious clinician.[13]

---

13. Sodium cyanid tablets containing 100 mg. may be obtained from Hynson, Westcott & Dunning, Charles and Franklin Streets, Baltimore. One of these tablets, when dissolved in 100 c.c. of sterile physiologic salt solution, yields a solution suitable for this work. In case the whole 100 c.c. is not used, it should be disposed of.

THE INFLUENCE OF LARGE DOSES OF THYROID EXTRACT ON THE TOTAL METABOLISM AND HEART IN A CASE OF HEART-BLOCK *

J. C. AUB, M.D., AND N. S. STERN, M.D.
BOSTON

The effect of the ingestion of thyroid extract on normal and myxedematous people has been studied by several observers. The general opinion seems to be that cases of myxedema and cretinism respond readily to thyroid extract by a considerable increase in basal metabolism, and that normal and obese people, while usually affected, respond to a less marked degree. DuBois[1] reports a case of cretinism whose basal metabolism rose 20 per cent. in three and one-half days under the influence of thyroid extract.

The amounts of thyroid extract employed differ greatly in the investigations on normal and obese individuals. A patient with obesity studied by Magnus-Levy[2] received the largest dose of thyroid extract that we know of — from 3 to 5 gm. daily for nineteen days. Anderson and Bergman[3] used large doses, but only for one day before observations. Thiele and Nehring[4] used doses up to 0.9 gm. a day.

Observations vary as to the influence of thyroid on the total metabolism of normal and obese people. Some investigators report an increase, others none. Magnus-Levy[2] found a rise from 10 to 25 per cent. following thyroid administration in three of five obese patients, and no rise in two. Stüve[5] is reported to have found a rise in one patient after thyroid. Anderson and Bergman,[3] after large doses the day before observation, found no rise in themselves except what they attributed to muscular exercise. Thiele and Nehring[4] affirmed that thyroid tablets in all their cases caused a rise of gaseous metabolism.

* Submitted for publication Aug. 24, 1917.

* From the Medical Service and Respiration Laboratory, Massachusetts General Hospital.

1. DuBois, E. F.: Metabolism in Exophthalmic Goiter, THE ARCHIVES INT. MED., 1916, **17,** 915.

2. Magnus-Levy: Untersuchungen zur Schilddrüsenfrage, Ztschr. f. klin. Med., 1897, **33,** 269.

3. Anderson and Bergman: Einfluss der Schilddrusen Futterung auf dem Stoffwechsel des Gesundes Menschen., Skand. Arch. f. Physiol., 1898, **8,** 326.

4. Thiele and Nehring: Untersuchungen des Respiratarischen Gaswechsel unter dem Einfluss von Thyreoideapparaten und bei Anaemischen Zustanden des Menschen, Ztschr. f. klin. Med., 1896, **30,** 41.

5. Stüve: Festschr., Frankfort a. M. 1896, **44.**

Means[6] found an increase in one obese patient, but two showed no rise after the administration of thyroid for five days. Jaquet and Svenson[7] found in some cases a rise in metabolism after thyroid, not in the basal observations, but in the extra energy given off following the ingestion of food. Their observations vary markedly from day to day, however, and the amount of thyroid given is not clear.

The present case is reported because of the marked effect of thyroid extract on the basal metabolism as well as on the auricular rate of the heart. It was possible to study auricles and ventricles separately owing to the presence of complete auriculoventricular dissociation.

REPORT OF CASE

History.—C. E. A., woman, white, single, aged 24, violin teacher. She had measles as a baby, and at 3 years scarlet fever and diphtheria simultaneously. She had no other infectious diseases. When 12 years old severe frontal headaches began which at first were biweekly, lasting from two to three days and associated with nausea, vomiting and abdominal pain. There have been no attacks for eight years. There has never been any syncope. She has been nervous and easily excited, quickly tired and never strong. She formerly felt cold all the time and had to wear extra clothes. Her skin and hair have always been dry.

Present Illness.—Eight years prior to admission she felt increasingly tired. Her arms began to ache, particularly the left; when worst, the pain occurred nightly and was so severe that she was kept awake and could not stand the pressure of the bed clothes. The attacks continue though gradually less severe.

For eight years she often noticed a sharp, severe pain in her left axilla, coming on after exertion. At times she had to stop walking because of severity of the pain and inability to breathe. About Nov. 1, 1916, a very intense attack seized her, but she kept on walking in spite of it. That night she could not move without pain.

During the previous seven years her physicians have said her heart rate was slow, usually 50. Her mother said she had an irregular heart when 12 years old. Seven years prior to admission her physician gave her thyroid extract without result. This was done because her dry skin, sensations of cold and general condition offered the suggestion of myxedema. Two years later she took 5 grains of thyroid every other day and improved, but she "usually got better in winter." In June, 1916, her physician, after consultation, decided to push the drug until symptoms appeared. He increased the dose until she took for two weeks 26 or 27 grains of Burroughs, Wellcome & Co.'s thyroid tablets a day, and for the next three weeks 28 grains a day. She said she had taken over 2,000 grains in from three to four months. Nevertheless, she had no tachycardia; her pulse was never over 72 and seldom over 62. She had no headache, exophthalmos, diarrhea, loss of weight or sweating. Her catamenia were normal, and sleep was good.

In November, her physician called Dr. Edsall in consultation, who suggested this investigation.

Nov. 6, 1916. Physical examination showed a quiet, well developed and nourished girl. Her hands revealed a slight tremor. Her thyroid gland was

6. Means, J. H.: Studies of the Basal Metabolism in Obesity and Pituitary Disease, Jour. Med. Research, 1915, **32** (new series 27), 121; The Basal Metabolism in Obesity, THE ARCHIVES INT. MED., 1916, **17**, 704.

7. Jaquet and Svenson: Zur Kentniss des Stoffwechsel Fettsuchtigen Individuen, Ztschr. f. klin. Med., 1900, **41**, 375.

not palpable. Her heart apex by percussion was 10.5 cm. to the left of the midline. The beat was forceful and the second sound sharp. There was a rather loud blowing systolic murmur everywhere. The heart was slow and block was suspected. The skin of her hands was soft and silky, her hair dry and fine. Her face was sallow and slightly coarse. Her eyes were not prominent. The basal metabolism was determined. Thyroid administration, 28 grains a day, was continued.

November 13. The hands were slightly swollen. The electrocardiograph confirmed the diagnosis of heart block. The basal metabolism was determined. Blood sugar 0.081 per cent. Thyroid continued.

November 16. Thyroid extract was omitted.

November 18. No thyroid was given on the third day. The basal metabolism was determined. Polygram (Fig. 1), electrocardiogram and roentgenogram were taken.

Roentgenographic report: Seven foot plate of the heart. The apex is 8 cm. to the left of the median line; right border is 5.3 cm. to right of the median line; total transverse diameter, 13.3 cm.; greatest transverse diameter of great vessels, 6.5 cm.; length of heart, 15.2 cm.; diameter at base, 10.4 cm.; enlargement of heart to the right. Prominence of auricle.

November 20. Basal metabolism determined. Blood sugar 0.09 per cent.

November 21. Wassermann test negative.

Fig. 1.—Polygram taken Nov. 18, 1916. Complete auriculoventricular dissociation. Auricular rate 108 per minute; ventricular rate 51 per minute.

December 4. No thyroid for nineteen days. She gets overtired now, cannot sleep, and feels cold all the time. Basal metabolism determined, and electrocardiogram taken (Fig. 2).

December 7. An attack of precordial pain, which radiated to her left arm, lasted several hours.

December 17. No thyroid for thirty-two days. Her skin is somewhat drier than before. Metabolism determined.

December 23. Electrocardiogram and polygram taken.

Jan. 27, 1917. Admitted to the Massachusetts General Hospital. Discharged February 4. Eight days prior to admission on climbing the stairs after one and one-half hours of violin practice, her heart began to beat forcibly, with an occasional strong beat, which her physician said was an extrasystole. This condition lasted a few days. This afternoon her left arm aches severely and she feels very tired.

Physical Examination.—The pupils were dilated but reacted normally; the heart apex was seen and felt in the fourth space 14 cm. to the left of midline and 3 cm. beyond the nipple; right border of dulness 2 cm. to right; her feet were cold; there was no tremor of the hands. The chart showed a range of pulse between 51 and 64. Urine and feces were normal; white count of blood, 16,700; differential count was normal.

January 28. The basal metabolism was determined. No thyroid in seventy-four days.

January 31. Electrocardiograms were taken before and after subcutaneous injection of one-fiftieth grain of atropin sulphate (Fig. 3).

February 1. Electrocardiograms were taken before and during right and left vagal and right ocular pressure, and immediately after walking 220 yards.

DISCUSSION

The basal metabolism determinations (Table 1) were made with the Benedict unit apparatus.[8] The patient was fasting at least fourteen hours and was at complete rest for at least one-half hour before, as well as during all observations. Every observation was checked by two observers.

The dose of thyroid ingested by the patient had been gradually increased by her physician until from 26 to 27 grains were taken daily for two weeks, and 28 grains a day for three weeks before she was seen by us and for ten days thereafter. She had thus taken about 1,000 grains in the course of five weeks, and over 2,000 grains in from 3 to 4 months.

As a result of these large doses, her average total basal metabolism was 54.5 and 52.3 calories per square meter per hour. These figures show a marked increase, 47 and 41 per cent., respectively, over the standard of 37 calories per square meter per hour found for a normal woman of her age. However, there were no other symptoms of hyperthyroidism than this increased metabolism and the increased auricular rate. There was no sweating, no nervousness, no diarrhea or exophthalmos. There was no loss of weight. On the contrary, she even claimed to have gained slightly.

After the omission of the thyroid the return to normal metabolism was very rapid. For sixty hours the metabolism continued at the same high level as before, namely, +40 per cent. But within the next forty-eight hours the metabolism dropped to +28 per cent. One week later, on the twelfth day after the omission of the drug, the metabolism had fallen to +11 per cent., a point practically within normal limits. Another week brought the variation to but 3 per cent. above normal.

As the height of the metabolism diminished the weight of the body increased, the net gain from November 13 to December 17 being 3.7 kg., about 8 pounds.

The respiratory quotients as obtained by the unit apparatus are not very accurate, and no great emphasis can be laid on them. Normally, they vary with a change in the percentage of foodstuffs burned. In this case they give no indication of a marked changed in the percentage of fat and carbohydrate utilized during and following thyroid ingestion.

Furthermore, there was no appreciable effect on the blood sugar by the thyroid medication. November 13, while thyroid was still being

8. Benedict, F. G.: Ein Universalrespirationsapparat, Deutsch. Arch. f. klin. Med., 1912, **107**, 156.

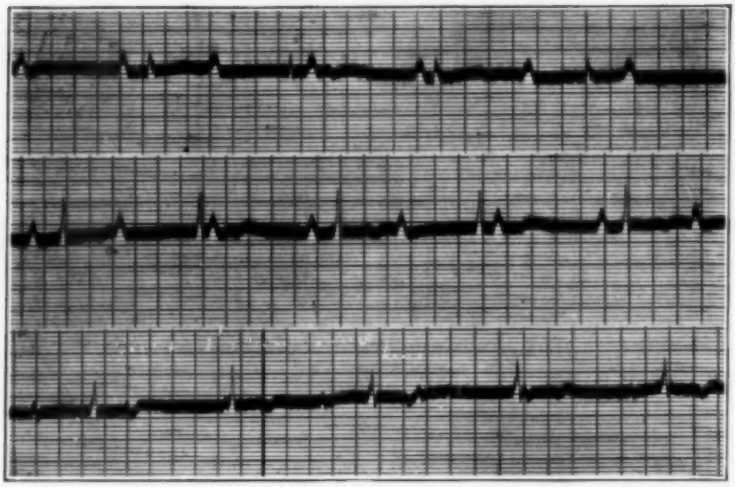


Fig. 2.—Electrocardiogram (Lead II), Dec. 4, 1916. Complete auriculoventricular dissociation; average auricular rate 71; average ventricular rate 50.

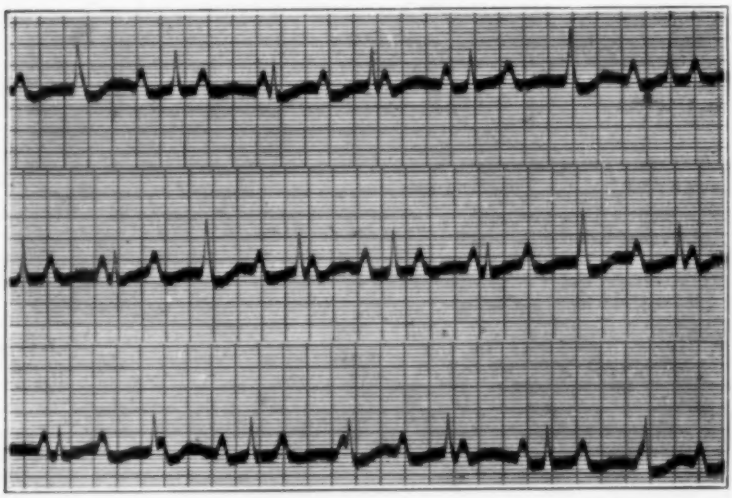


Fig. 3.—Electrocardiogram (Lead II), Jan. 31, 1917. Forty minutes after the subcutaneous injection of one-fiftieth grain of atropin sulphate. Auricular rates: upper record 116, middle record 135, lower record 120; average ventricular rate 74.

TABLE 1.—METABOLISM DATA

Girl aged 24 years. Height, 157 cm. Normal Metabolism, 37 calories per square meter per hour.

Date	Average Pulse	Weight, Kg.	Surface Area Height and Weight Chart	CO_2 per Minute, C.c.	O_2 per Minute, C.c.	Respiratory Quotient	Average Total Calories per Hour	Average Calories per Square Meter per Hour	Variation from Normal Standard, per Cent.	Thyroid Administration
11/ 6/16	57	....	....	229	285					
	60	....	....	223	295					
	56	....	....	227	285					
Average	58	53.0	1.52	226	288	0.80	82.9	54.5	+47	28 grains a day
11/13/16	55	....	....	229	269					
	55	....	....	236	279					
Average	55	54.0	1.53	233	274	0.85	80.0	52.3	+41	Still taking 28 grains a day
11/18/16	55	....	....	212	276					
	54	....	....	216	281					
Average	55	54.5	1.54	214	278	0.77	79.6	51.7	+40	Thyroid stopped after November 15. No thyroid the third day
11/20/16	54	....	....	218	241					
	53	....	....	226	248					
Average	54	53.5	1.53	222	244.5	0.91	72.7	47.3	+28	No thyroid the fifth day
11/27/16	56	....	....	192	215					
	53	....	....	192	216					
Average	55	55.5	1.55	192	216	0.89	63.7	41.1	+11	No thyroid the twelfth day
12/ 4/16	52	....	....	168	203					
	52	....	....	165	205					
Average	52	55.5	1.55	167	204	0.82	59.2	38.2	+ 3	No thyroid the nineteenth day
12/17/16	49	....	....	185	224					
	48	....	....	189	236					
Average	49	57.7	1.57	187	230	0.81	66.4	42.3	+14	No thyroid the thirty-second day
1/28/17	64	....	....	176	221					
	61	....	....	170	217					
Average	63	57.3	1.57	173	219	0.79	62.8	40.0	+ 8	No thyroid the seventy-fourth day

administered, the blood sugar was 0.081 per cent., and November 20, five days after omission of the drug, the blood sugar was 0.090 per cent., both normal figures.

From the cardiac point of view the case is one of the few of complete auriculoventricular dissociation in which the ventricular rate is 50 or over. Several cases in the literature show a high ventricular rate when the dissociation was due to digitalis poisoning, but only a few in which the cause of the block was organic. Lea,[9] Hunt,[10]

TABLE 2.—Electrocardiographic Rates

	Average Auricular Rate	Average Ventricular Rate	Remarks
11/13/16	119	57	Thyroid 28 grains a day
11/18/16	102	58	No thyroid for 2 days
11/20/16	100	57	No thyroid for 5 days
12/ 4/16	71	50	No thyroid for 19 days
12/23/16	75	55	No thyroid for 38 days
1/31/17	108* 96 110	103	65	Before atropin
1/31/17	116 125 120	124	74	After atropin, gr. 1/50
2/ 1/17	75	56	Normal
2/ 1/17	75	56	During right vagal pressure
2/ 1/17	75	56	During left vagal pressure
2/ 1/17	75	55	During right ocular pressure
2/ 1/17	73	55	Immediately after walking 220 yards

* Auricular rates before and after atropin, as determined by the electrocardiograph.

TABLE 3.—Polygraphic Rates

11/18/16	106	51
12/23/16	77	49
1/28/17	70	50

Windle,[11] Neuhoff[12] all report cases of complete auriculoventricular dissociation in which the ventricles beat at a rate of from 50 to 60 per minute, and even higher under certain circumstances.

The present case showed variations in pulse rate from 48 to 64 at the times of the metabolism studies. The electrocardiograph showed

9. Lea, Edgar: Complete Heart-Block with Higher Ventricular Than Auricular Rate, Lancet, London, 1915, **1**, 1289.
10. Hunt, G. H.: Exhibition of Clinical Case, Lancet, London, 1913, **1**, 1312.
11. Windle, J. D.: Permanent Complete Heart-Block, Heart, 1910, **2**, 102.
12. Neuhoff, S.: Complete Heart-Block with Rapid, Irregular Ventricular Activity, Am. Jour. Med. Sc., 1913, **145**, 513.

variations in the ventricular rate from 50 to 65, and forty minutes after the subcutaneous injection of one-fiftieth grain atropin sulphate, an increase to 74.

The auricles, when the patient was still under the influence of thyroid, beat at the rate of 119. November 18, three days after thyroid was omitted, the auricular rate had fallen to 102, two days later to 100, and by December 4, the nineteenth day after stopping the thyroid, to the normal rate of 71. Thereafter the auricular rate was constantly about 75, except on January 31, when for some unexplained reason — perhaps excitement — it rose to an average of 103 at the same time as the ventricular rate rose to 65. The next day the auricles beat regularly at 75.

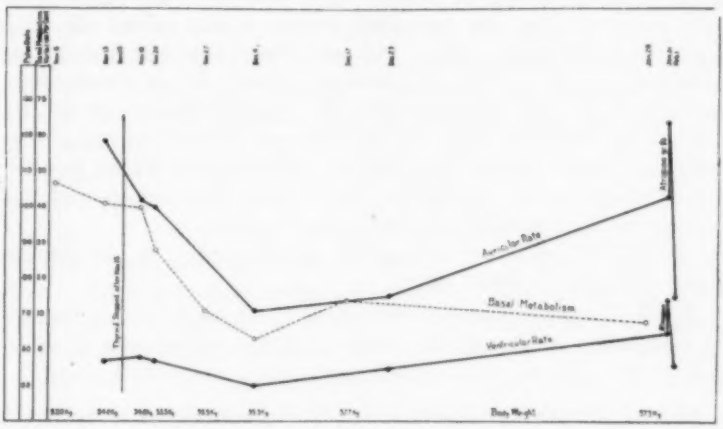


Fig. 4.—The influence of large doses of thyroid extract on the total metabolism and heart in a case of heart block.

The auricular rate curve and the metabolism curve (Fig. 4), though drawn to different scale, show a parallelism that is worthy of note.

The fact that the auricular rate was definitely modified by the ingestion of thyroid to give an auricular tachycardia, while the ventricular rate was in no wise influenced, seems to indicate that thyroid substance produces tachycardia through nervous channels and not by direct action on the muscle.

The subcutaneous injection of one-fiftieth grain atropin sulphate affected the rate of both auricle and ventricle. The auricles beat at the high rate of 135 (average 124) instead of at the previous high rate of 110 (average 103), an increase of about 23 per cent. (average 20 per cent.). The ventricular rate rose from 65 to 74, an increase of about

14 per cent. According to Frédéricq,[13] this latter indicates that the heart-block is not absolute, that some vagus fibers, whose terminal filaments were paralyzed by the atropin, had been exerting an inhibitory action on the ventricles. Other mechanisms, however, are conceivable by which the phenomenon might be explained.

Right and left vagal pressure, right ocular pressure, and exercise produced no effect on either auricles or ventricles.

SUMMARY

A case of complete auriculoventricular dissociation is reported for the following reasons:

1. Thyroid extract was administered in increasing doses so that by the end of a period of from three to four months over 2,000 grains had been ingested. For the last four weeks of this period the dose amounted to 28 grains a day. The only effects observed from taking these large amounts of thyroid were an increase in the basal metabolism of 47 per cent. above normal and a rapid auricular rate of 120. After the withdrawal of the thyroid the basal metabolism fell to normal limits within twelve days and the auricular rate within nineteen days (perhaps less). During the first months after the thyroid was omitted the body weight increased over 8 pounds.

The thyroid administration had no apparent effect on the respiratory quotient or the blood sugar.

2. The auricular rate was influenced by thyroid extract, but not the ventricular, which suggests that thyroid does not increase the heart beat by direct action on the muscle, but through nervous channels.

We wish to express our thanks to Dr. Edsall for permission to make these studies of his patient, and for his constant stimulating interest; and to Drs. J. H. Means and P. D. White for valuable aid and suggestions.

13. Frédéricq, Henri: Critique de l'emploi des éprouves de l'atropine et du nitrite d'amyle dans le diagnostic des bradycardies, Arch. d. mal. du coeur, Par., 1916, **9**, 377.

EXTENSIVE CALCIFICATION OF THE LUNGS AS A DISTINCT DISEASE *

FRANCIS HARBITZ, M.D.
Professor of Pathology, University of Christiania, Norway

Calcareous deposits, especially local, are of frequent occurrence in degenerated and necrotic tissue, old inflammatory exudates, and other dead material such as thrombi. Calcification in the media and intima of the arteries in old persons, in pleural and pericardial exudates where large calcareous plates may form, the concretions in the apices of the lungs and in the bronchial lymph nodes as the result of tuberculosis, are all familiar examples. Wherever tissue degenerates, deposits of calcium salts may take place, usually in the stroma, but also, although rarely, in the cells themselves, as, for instance, in the renal epithelium in toxic necrosis, in ganglion cells, in muscle fibers. Deposition of calcium salts also occurs on a larger scale, when it may give rise to peculiar conditions and even distinct diseases. The cause of such deposits is in general assumed to be a supersaturation, so to speak, of the blood and tissue fluids with calcium salts. If the normal elimination of calcium by way of the intestinal tract and the kidneys is disturbed as, for instance, on account of nephritis, calcareous deposits occur more readily. Added to this we have the facts that certain organs and tissues are predisposed to calcareous infiltration, namely, the lungs, the endocardium of the left ventricle, the pulmonary veins, the gastro-intestinal mucous membrane and the kidneys, as shown in 1885 by Virchow, who described calcareous infiltrations of these organs in diseases of bones in the course of which calcium salts are set free, more particularly in bone tumors, either primary or secondary, but also in osteomalacia and in leukemic conditions. Virchow called this process lime or calcium metastasis. It is believed that a lowered acidity of the blood in these organs and tissues may account for their predisposition to calcific deposits. According to Wells,[1] some thirty-six cases of extensive, and, as a rule, multiple, calcareous "metastasis" had been described up to 1915; since then some additional cases have been reported. Still different are the cases in which deposition of lime salts takes place primarily in certain tissues or organs in persons who do

* Submitted for publication Sept. 3, 1917.

1. Wells, H. G.: Classification and Ossification, THE ARCHIVES INT. MED., 1911, **7**, 721. Metastatic Calcification, Ibid., 1915, **15**, 514. These articles contain references to the literature.

not appear to suffer from any other disease except such peculiar deposits. A form of this condition is infiltration of calcium salts in bursae, tendon sheaths, etc., which may occur as an independent process and cause more or less severe disturbances of function. A number of cases of this kind have been described recently in Norway by Paus and Natvig (subacromial bursa), and by Sinding-Larson and Kjerschow (subepichondal bursa). In these cases there was found in the bursae white, chalky masses or a milky fluid with smaller, hard concretions and incrustation of the surrounding tissues, the masses consisting principally of carbonates and phosphates of calcium. In the tissues were chronic inflammatory changes with indefinite giant cells, enclosing small calcareous masses, but no demonstrable primary necrosis; on the inner wall of the bursae were small papillomatous outgrowths. A rare but also more serious condition is "calcinosis universalis," cases of which have been described recently, which is a chronic affection, especially of young persons, sometimes of several children of the same family, but also of older persons. Phosphates and carbonates of calcium are deposited as nodular or band-like formations, or as softer, crumbling or even confluent material, especially in the subcutaneous tissue as well as in bursae, tendons, muscles, about nerves, and often in symmetrical form. As a rule the internal organs are not involved and the joints and bones appear to be normal. Over affected parts the skin may be pigmented and hard. Various vasomotor changes have been observed. The upper as well as the lower extremities and also the trunk may be affected. Muscular atrophy takes place and invalidism in different grades results. External irritation, injury or rheumatic attacks may hasten the depositions, which also may take place in paroxysms with fever, swelling, redness and tenderness of the parts involved. As a rule, however, the process is gradual. If a softening takes place, with secondary infection, death may result from septicopyemia. There appears to be no primary degeneration in the connective tissue or elastic elements, which are especially affected, and it seems reasonable to assume that it concerns a metabolic anomaly of an unknown nature.

The following case under the care of Dr. Winge is an illustration:

A woman, 63 years old, suffered many years until the hands and fingers became greatly deformed and enlarged on account of extensive deposits around all the joints; there was a fluctuating swelling on one buttock as large as half a hen's egg, which on incision was found to contain a liquid and semisolid, clumpy, white material, extending along the subcutaneous tissue through fascia and muscles clear to the bone, so that it was not possible to make a complete removal. A clump 4.5 by 7.5 cm., white as chalk and irregular, was removed and found to contain carbonate, phosphate and a little oxalate of calcium.

Morbid infiltration with calcium salts without evident cause may take place also in internal organs, and I have examined a remarkable

case of most extensive calcareous deposition in the lungs, which it is my special purpose to report:

History.—The patient was a woman, 41 years old, a workingman's wife, admitted to the service of Prof. P. F. Holst, Feb. 10, 1917. The family history was good; no children. While a child and also three years prior to admission, she had acute rheumatism, the last attack being rather mild; for some time she had had dyspeptic symptoms, pain in the region of the stomach, and during the previous three years several rather large hemorrhages from the stomach; occasionally she would have severe nose bleed, and once it was very extensive; menstrual bleeding was also severe. During the previous ten years she would get out of breath easily, and recently dyspnea would come on readily at the same time that the face seemed to become blue. In the summer and fall of

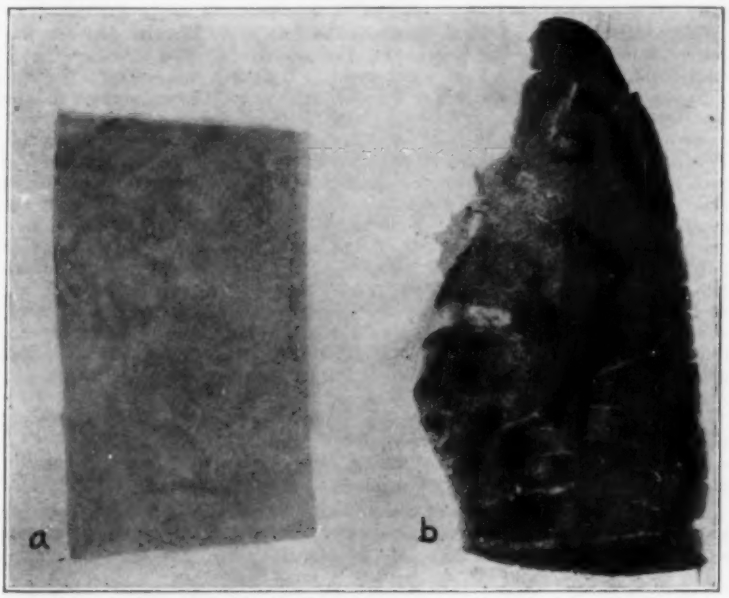


Fig. 1.—Roentgenograms of sections of the same thickness of normal lung (*a*) and calcified lung (*b*).

1916 the legs became edematous; at Christmas time the edema returned, and at the same time the abdomen became large, the urine small in amount and deeply colored, and from then on dyspnea forced her to sit up in bed at night.

Examination.—On admission the face was cyanotic, there was anasarca, the finger tips were club-shaped; pulse 104, respirations 34; prolonged expiration, especially over the left lung; at the base of the lungs, fine crepitation; heart somewhat enlarged, especially to the right; loud systolic murmur, most marked at the apex, with accentuation of the second pulmonary sound; blood pressure 110; liver enlarged; ascites; urine of specific gravity of 1.032, no albumin, blood or sugar.

A few days later the blood showed 8,448,000 red corpuscles and 11,600 leukocytes.

Under treatment with digitalis and theobromin sodium salicylate the edema diminished and the urine increased in amount, but before long the edema again increased, also the cyanosis, the heart action became irregular, and the patient died suddenly, March 3.

Necropsy.—The postmortem showed cyanosis and edema of the legs. The heart was enlarged, weighing 400 gm., the enlargement involving practically exclusively the right side; the heart muscle was normal; valves normal, and the coronary arteries only a little sclerotic and not narrow; the aorta was normal, without calcareous deposits.

There was no fluid in the pleural cavities; a few fibrous bands were present over the left lung and general adhesions over the right; the lungs were large, as in croupous pneumonia, solid and heavy, feeling like stones and sinking in water; the right lung weighed 2,750 gm., the left 2,130, in all 4,880 gm. Placed on the base, the lungs stood by themselves; in consistency the substance was almost like wood, but not uniformly so, being apparently full of small, solid particles, and under the pleura here and there were small, white, flat masses of mineral nature. The substance could be cut only with difficulty and felt like porous bone. Passing the finger over the surface felt like rubbing it over sandpaper, and here and there were round or irregular concretions. The distribution of mineral matter was about the same in both lungs, perhaps a little more marked in the left. The cut surface was peculiar, reddish-brown, with numerous small holes in an extensive stroma; bloody, frothy fluid exuded, The first impression that the lungs were free of air and compact was not correct; air was present everywhere, but the air-containing tissue was less in amount than the interstitial tissue with the mineral deposits. Areas in the anterior border of the right lung and the anterior surface of the upper lobe contained more air than other parts of the lungs. After drying a small slice of lung substance it had a peculiar yellow red color and a porous surface which felt like sandpaper and from which small calcareous granules would fall out. In both apices, at the hilus of the lungs and in the lymph nodes in the neck, were small, old caseous foci. The pulmonary arteries were sclerotic but not calcified or dilated; the pulmonary veins were normal. No calcification was present in the larger bronchi, trachea, or larynx.

Mouth, pharynx and esophagus were normal.

The thyroid gland was rather large; weight 29 gm.; parathyroid glands not enlarged; no traces of the thymus.

The peritoneal cavity contained 900 c.c. clear yellow fluid; lining smooth.

Spleen, liver and kidneys were passively congested.

Microscopic Examination.—Microscopically there were no changes in the kidneys, except that the glomeruli were quite cellular and that under the capsule were occasional linear infiltrations of round cells.

In the surface of the left adrenal was a small concretion.

The ovaries were small and fibrous; tubes tuberculous, containing caseous material and tubercles in the mucosa.

No ulcers or definite scars were found in the stomach, the mucosa of which was normal under the microscope.

The hypophysis, which was large and weighed 1.1 gm., appeared normal on microscopic section.

The spinal column, ribs, femur, sternum and cranial bones were normal so far as could be determined on careful gross and microscopic examination.

Frozen sections of the lungs showed numerous round and oval concretions in the interstitial tissue, and compression of the alveoli. In decalcified section the concretions have a lamellated structure, concentric, there being no needle shaped crystals or larger masses; the clumps lie in the interalveolar tissue and encroach on the alveolar spaces (Fig. 2). The stroma is increased in amount, in places sclerotic, also anthracotic and infiltrated with round cells. The veins and capillaries in the septa are dilated and there are hemorrhagic infiltrations

into the septa as well as into alveoli and small bronchi. In places the alveoli appear as narrow clefts; in other places as small spaces with swollen desquamated cells, and then again as large spaces, the lungs being not totally solid anywhere. The larger vessels and the bronchi appear normal. There were no signs anywhere of old diffuse inflammatory processes, such as chronic bronchitis or pneumonia. On addition of sulphuric acid to frozen sections, typical gypsum crystals formed; of hydrochloric acid, gas bubbles. Chemical analysis (H. Siebke) gave 78.05 per cent. ash, of which 18.3 per cent. consisted of calcium carbonate and about 80 per cent. of calcium phosphate, as well as small quantities of iron, magnesium, etc.

The extensive lime deposits in the lung in this case, so extensive that it seems quite remarkable that life lasted as long as it did, do not appear to be duplicated by any reports in the literature either of genuine "metastatic" deposits or of the few cases in which there was no definite cause. It is noteworthy that the lungs weighed nearly six times as

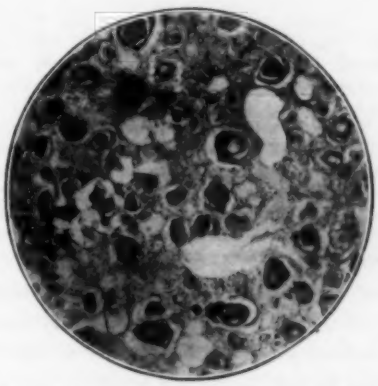


Fig. 2.—Photomicrograph of decalcified section of calcareous lung: between the large alveolar spaces numerous round, concentrically constructed calcareous clumps are seen.

much as normal and that on first impression they appeared to be almost entirely airless; the deposits were diffuse and evenly distributed throughout the lungs, showing that they were independent of local changes such as thrombi or infarcts.

For purposes of comparison I wish to mention briefly certain cases of calcification of the lung which I have found in the literature. These may be devided into two groups, (1) the metastatic, dependent on bone destruction, and (2) cases like the one I have described in which there were no indications of bone disease.

1. In addition to a number of cases of metastatic calcification, some of moderate degree only, described by Virchow, Kockel, Askanazy and others, I would mention especially the following cases: The case described by Tschistowisch and Kollesnikoff of extensive calcium

metastases in the lungs and other organs associated with multiple myeloma; the lungs were large, very heavy, hard, dry, the surface grayish-white and rough, due to deposits in the walls of the alveoli and around the blood vessels. Pari's case in a patient who died from cancer of the uterus with bone metastases, in which there was general calcification of the lungs, the surface was coarsely porous, dry, grayish-white and rough, there being also present larger, more completely calcified areas. And in the instance described by Wells, who mentions the cases just cited, of extensive calcification in the heart and lungs in a case of myologenous leukemia, the lungs were heavy, solid and felt sandy.

In this group probably belongs the following case, the facts in regard to which I obtained through the courtesy of Professor Quensel in Upsala and Dr. Hellman:

> The patient was a woman, 65 years old, who died with symptoms of intestinal obstruction and marasmus. The lungs were enlarged, grayish-red and looked as if powdered; on removal they retained their form, were solid and heavy but floated in water; finger depressions remained. The cut surface seemed as if dusted with fine sand and a grayish-red frothy fluid could be pressed out. The heart, kidneys, liver and spleen seemed normal. The mucous membrane of the stomach was dark red and showed numerous small depressions surrounded by narrow, less deeply colored elevations, but whether this was due to calcification was not determined. The intestines were normal; there was coprostasis. The cranium was normal in form and thickness but very soft, consisting mostly of diploe, and both the surfaces showed irregular dark-red and grayish-white spots. The brain and its membranes were normal.

There was here a diffuse and extensive calcification of the lungs and possibly also of the stomach, due most likely to a primary disease of the bone, as indicated by the appearance of the cranium; but the exact nature of this disease we do not know.

As examples of the second group, I would mention the case in which Virchow found grayish-white incrusted nodes as large as nuts in one lobe in a woman, 43 years old, with chronic pleuritis and nephritis, but no disease of the bones; Chiari's case in a woman, 27 years old, with gastric ulcer and general marasmus, half of the right lung being hard, grayish-white, grating on section; microscopically, there were calcareous deposits in the wall of the alveoli and in the vessels; there were also a few calcareous foci in the left lung and calcification in both kidneys; bones normal. Hlava also found calcification in spongy form, of the right upper lobe, especially, in a person who died with circulatory disturbances. Kockel described microscopic calcification in the lungs in a number of cases in some of which there was heart disease; while Kischensky found advanced calcification in part of one lung in a woman with chronic nephritis, amyloid disease, but with no changes in the bones. Here belongs also the case described by Stade, who found an extensive deposit of calcium salts in the lungs of a man,

44 years old, who died with pneumonia and who had no changes in the bone system. The substance of the lung was rough like sandpaper, solid, and microscopically the calcification was extensive.

We see that in no case of either group was there so extensive and complete a calcification of the lungs as in the one I have described. Usually the calcification seems to have been rather limited, sometimes strictly local, but there are cases in which it was diffuse, as, for example, in the case described by Virchow as follows: "Lungs mostly grayish-white, resistant, especially at the borders of the lobules, calcified; cut surface porous like a sponge, with small holes, dry, rough; alveoli everywhere, large and wide." The cases described by Pari, Stade and Wells are also characterized by extensive deposits.

In regard to the cause of calcification in the lungs, it appears that in most cases it may be regarded as metastatic in Virchow's sense, that is, as secondary to some form of destructive bone disease, with solution of the calcium salts in the bone and secondary deposition in other tissues. In some cases the evidence of bone destruction is not definite. In a small group, however, there is not the slightest evidence of any bone destruction; this would seem to be especially true in my case, in which several bones were carefully examined with this point in view. In my case the kidneys were also normal, so that there is no reason to believe that there was any interference with calcium elimination by way of the urine. Neither were there any extensive changes in the stomach or intestines, the most important places of calcium elimination; so that we are without any indications that in this case diminished calcium excretion was the reason of the calcification in the lungs. The question arises whether there were peculiar degenerative or dystrophic conditions in the lungs which would induce precipitation of calcium salt, as is believed is the fact in necrotic and degenerated tissue. In this case such changes would have had to be diffuse, and there is no evidence that such changes were present. The dyspnea and cyanosis, which were noticed for many years, may have been the result of the calcification; possibly calcification might result from chronic stasis and secondary nutritive changes in the walls of the alveoli, but there is no way to account for any primary stasis in this case, as the condition of the heart clearly was secondary and there was no sign of previous disease in the lung, such as interstitial pneumonia, on the basis of which calcification might have taken place. The possibility that some organ with internal secretion was at fault must be considered — the parathyroid glands, the thyroid, the hypophysis, the thymus, and the ovaries. There is evidence that the parathyroid glands influence calcium metabolism; removal of these glands increases elimination of calcium and disturbances of ossification. In osteomalacia, rickets and senile osteo-

porosis, tumors and other changes have been found in the parathyroid glands. In my case, however, there were no changes in the parathyroids, the thyroid, thymus, or hypophysis. Whether any significance is to be placed on the fibrous condition of the ovaries in this case is indeed a question. We know but little of the influence of the ovaries in calcium metabolism. The ovaries are frequently fibrous in young women in whom there are no demonstrable disturbances of calcium elimination or metabolism. Taking it all in all, there are in this case no changes in the internal organs to explain the calcification in the lung. It would seem, then, that one is driven to assume that in such cases as I have described there is a "constitutional anomaly" or metabolic disturbance of unknown nature, in consequence of which calcium salts are deposited from the blood in apparently normal tissues, and especially in the lungs, perhaps on account of the low acidity of the blood as it gives up carbon dioxid.

AURICULAR FLUTTER *

JOHN M. BLACKFORD, M.D.
SEATTLE, WASH.
AND
FRED A. WILLIUS, M.D.
MAYO CLINICS, ROCHESTER, MINN.

Sixteen cases of auricular flutter have been observed in the Mayo Clinic by us during the last thirty months. In the study of these cases a review of the literature revealed certain features which made it seem desirable to record our findings. The paucity of case reports in the literature is ample evidence that the condition is frequently overlooked.

Definition.—Auricular flutter may be described as an acceleration of the auricles to a rate beyond 200 per minute.[1] In all reported cases such acceleration has been accompanied by a partial heart block, giving a ventricular rate of one-half, one-third or one-fourth of the auricular rate, or a total dissociation of rhythm (complete heart block); or the degree of block may vary between the auricular beats, giving a gross ventricular arrhythmia. The partial block is apparently due to the inability of the auriculoventricular bundle to conduct impulses so rapidly, or to the inability of the ventricle to respond so rapidly. There is no reason to suppose that organic disease exists in the bundle except in those few cases (two, one our own, reported to date[2]), in which there is evident complete dissociation; and in a small group of ventricular bradycardias in which the auriculoventricular bundle may at least be questioned. In the paroxysmal attacks, when the ventricles assume the full auricular rate, we have evidence of a temporary increase in irritability of the ventricle or the auriculoventricular bundle.

There is no known pathologic difference between an auricular rate of less than 200 and one at which the rate exceeds this figure, yet the clinical manifestations are so different as to justify the classification of flutter as a clinical entity.[3] The fundamental clinical differences

* Submitted for publication Sept. 20, 1917.

1. Hertz, A. F., and Goodhart, G. W.: The Speed-Limit of the Human Heart. Quart. Jour. Med., 1908-1909, **2**, 213.

2. Jolly, W. A. and Ritchie, W. T.: Auricular Flutter and Fibrillation. Heart, 1910-1911, **2**, 177.

3. Lewis, T.: Observations on a Curious and Not Uncommon Form of Extreme Acceleration of the Auricle. "Auricular Flutter." Heart, 1912-1913, **4**, 171.

lie in the fact that flutter tends to persist indefinitely, whereas auricular paroxysmal tachycardia rarely reaches so rapid a rate and the attack stops after a relatively short period. In flutter the auricles continue their rapid rate when the ventricles are slower, while in auricular paroxysmal tachycardia 1-1 rhythm is always present and the sinus rhythm is restored between attacks.

Experimental.—Auricular flutter was produced experimentally by MacWilliam in 1887[4] by mild faradization of the auricles of exposed animal hearts. Lewis (1912-1913) observed the same condition after the intravenous injection of glyoxylic acid.[5] Hirshfelder[6] (1908) produced it by ligation of the coronary arteries, and similar observations have been made after cooling the auricles and during chloroform anesthesia. In our laboratories, working with Kendall, we produced, experimentally, hyperthyroidization in the goat by a large injection of the thyroid active principle, alpha-iodin.[7] We have observed auricular flutter as one of the cardiac phenomena shown by practically continuous electrocardiographic tracings over several hours preceding death.

Mechanism.—Flutter is caused by focus of stimuli in the wall of the auricular muscle at a point outside the normal pacemaker or sinus node (ectopic stimuli), the discharge of stimuli being at a rate so rapid and continuous as to submerge the sinus activity. This conclusion is based on the fact that the P wave is found to have an abnormal form in the clinical electrocardiogram and that in the experimental study the P wave approaches the normal contour as the stimulus is applied nearer the sinus node.

A statement of methods by which flutter can be produced in the laboratory will help to visualize the subject. A single shock applied with the stimulating electrode to any point in the wall of the auricle causes an auricular extrasystole, providing the stimulus is applied when the muscle is not contracting. A continued mild faradization applied to the same point causes similar contractions, but each contraction is maximal, and hence only when the muscle begins to relax, or pass out of the "refractory phase," is further stimulation effective; then another contraction is caused by succeeding stimulus, etc. In

4. McWilliam, J. A.: Fibrillar Contraction of the Heart. Jour. Physiol., 1887, **8**, 296.

5. Lewis, T.: The Mechanism of the Heart Beat with Special Reference to the Clinical Pathology. London, Shaw, 1911, p. 311.

6. Hirschfelder, A. D.: Contributions to the Study of Auricular Fibrillation, Paroxysmal Tachycardia, and the so-called Auriculo-(atrio) Ventricular Extrasystoles. Bull. Johns Hopkins Hosp., 1908, **19**, 322.

7. Kendall, E. C.: The Isolation in Crystalline Form of the Compound Containing Iodin which occurs in the Thyroid; its Chemical Nature and Physiological Activity. Tr. Assn. Am. Phys., 1915, **30**, 420.

other words, the auricle is contracting as rapidly as possible—a state of "flutter" during the time continuous faradization is applied.

Thus, if asphyxia is allowed to act, a visible change is found in auricular activity. Suddenly the auricle dilates and ceases coordinate contraction, but each little individual muscle bundle begins to contract regardless of the muscle mass; that is, incoordinated contraction. In other words, multiple foci of irritability occur throughout the auricular mass due to asphyxiation. The dilated auricle as a whole is functionless. It acts only as a reservoir, but close inspection reveals the fibril-

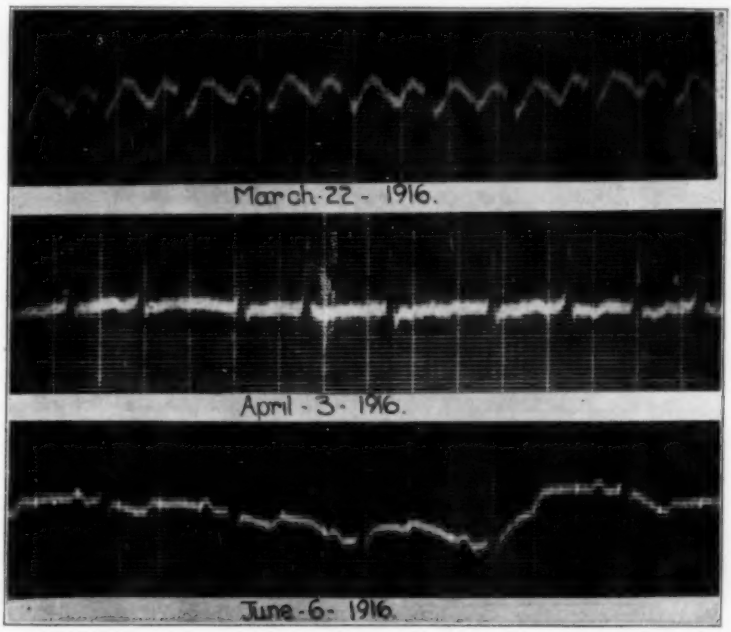


Fig. 1 (146153).—1. Typical auricular flutter. 2. Fibrillation induced by digitalis. 3. Normal rhythm following thyroidectomy.

lating muscle twitching which is characteristic of auricular fibrillation, and the total arrhythmia of the ventricular action is at once apparent.

In the human heart the irritable focus causing flutter must be the result of disease. It cannot be too strongly emphasized that flutter, per se, is only objective evidence of localized irritability in the auricular wall; and that any other organic cardiac disease may exist in the same heart.

It is evident that at present no clear distinction, mechanical or organic, can be given as differentiating paroxysmal auricular tachycar-

dia from auricular flutter. The difference is largely a well-grounded clinical conception based on a different symptomatology. The only objective distinction is one of auricular rate, and that a partial block usually exists in flutter cases.

Pathology.—It is already evident that auricular flutter is not a pathologic entity, for we often see auricular extrasystoles, flutter fibrillation and a sinus rhythm in a single case within a relatively short time. The literature contains only six necropsy reports in unquestioned cases; our series contains two others. Ritchie[8] has reported a lymphocytic infiltration of the epicardium, most marked in the region of the sinus node; and he thinks this may have depressed sinus activity. The cases of Gulland and Mackenzie,[9] and Hume's[10] first case add nothing significant to these findings. The pathologic findings are at present unimportant, since so little has been recorded.

The irritable auricular focus is the essential feature, and our study must include all causes of localized injury or irritability to heart muscle. Such causes may be classified under three heads: (1) infections causing localized injury; (2) general and local myocardial degeneration from any cause, as hypertension, valvular disease, goiter, etc.; and (3) localized malnutrition of the auricular wall as in coronary sclerosis, etc.

We do not know why in certain cases a localized injury should be selected from more extensive myocardial damage to become a source of irritation, and to send forth such rapid impulses as to submerge the sinus rate and establish flutter. That such functional pathology exists, however, is evident.

We have no evidence that flutter can be purely of neurogenic origin. In all the reported cases and in our own cases there was either objective evidence of other cardiac damage or a history indicating infectious, toxic, myocardial or coronary etiology.

Etiology.—Auricular flutter occurs four times as often in men as in women, counting the reported cases and our own. The average age of the patients was 47 years, the youngest 6 years and the oldest 82 years. The condition is most frequent between the ages of 40 and 60 years, but in our series more cases[7] occurred between 30 and 40 years of age.

---

8. Ritchie, W. T.: Further Observations on Auricular Flutter. Quart. Jour. Med., 1913-1914, **7,** 1.

9. Mackenzie, J.: Diseases of the Heart. Ed. 3, London, 1913, p. 105.

10. Hume, W. E.: A Polygraphic Study of Four Cases of Diphtheria with a Pathological Examination of Three Cases. Heart, 1913, 1914, **5,** 25.

Our cases at once call attention to an etiology of infection, since antecedent diseases of probable streptococcic origin were noted with remarkable frequency, namely, 1 rheumatic fever, 5 tonsillitis, 6 bad teeth, 6 "grippe," 2 pneumonia. In 3 cases the patient dated his symptoms from one of these infections. All the patients in our series gave histories of one or more of the foregoing diseases. In 59 reported cases there is little data on this phase of the subject, but when given, the streptococcus group predominates; thirteen histories of rheumatic fever are recorded.[11] Venereal disease plays no evident part.

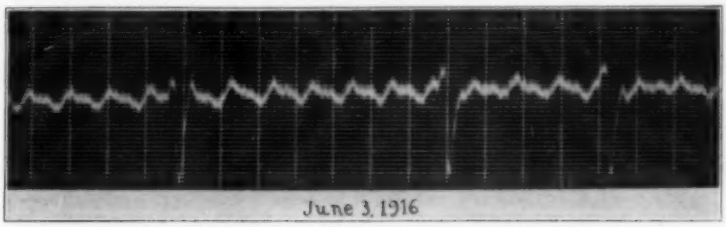


Fig. 2 (161186).—Auricular flutter with heart block; auricular rate 260; ventricular rate 43.

None of our patients was syphilitic, though three cases are noted in the literature.[12] We noted four histories of typhoid fever; other reports contained one case.[13]

Exophthalmic goiter was definite in four of our cases and was believed to be the probable etiologic factor. One other such case is reported.[14] Mitral disease was observed in but one of our sixteen

11. Mathewson, G. D.: A Case of Auricular Flutter. Edinburgh Med. Jour., 1913, **11,** 500. Ritchie, W. T.: Further Observations on Auricular Flutter. Quart. Jour. Med., 1913-1914, **7,** 1. Gunson, E. B.: Auricular Flutter Followed by Paroxysmal Auricular Fibrillation. Lancet, London, 1914, **2,** 151. Levine, S. A., and Frothingham, Jr., C.: A Study of a Case of Auricular Flutter. THE ARCHIVES INT. MED., 1915, **16,** 818. Neuhof, S.: Auricular Flutter Accompanying Acute Endopericarditis. Med. Rec., New York, 1915, **88,** 995. Tallman, M. H.: Auricular Flutter. Northwest Med., 1916, **15,** 145. Sutherland, G. A.: Auricular Flutter in Acute Rheumatic Carditis. Brit. Jour. Child. Dis., 1914, **11,** 337. Ritchie, W. T.: Auricular Flutter. Edinburgh, Green, 1914, p. 33. Mackenzie, J.: Diseases of the Heart. Ed. 3, London, 1913. Appendix, Cases 68 and 69. Quoted by Ritchie, Footnote 14.

12. Gunson, E. B.: Auricular Flutter Followed by Paroxysmal Auricular Fibrillation. Lancet, London, 1914, **2,** 151. Ritchie, W. T.: Auricular Flutter. Edinburgh, Green, 1914, p. 33. Cowan, J.: Diseases of the Heart. London, Arnold, 1914, p. 205.

13. Tallman, M. H.: Auricular Flutter. Northwest Med., 1916, **15,** 145.

14. Ritchie, W. T.: Auricular Flutter. Edinburgh, Green, 1914, p. 33. Sutherland, G. A.: Auricular Flutter in Acute Rheumatic Carditis. Brit. Jour. Child. Dis., 1914, **11,** 337.

patients, though the literature[15, 2] reports ten cases of stenotic or double mitral lesions.

Relative Incidence.—We examined electrocardiographically 3,500 patients and observed 16 auricular flutter records. There were 363 patients with auricular fibrillation, 160 showing auricular extrasystoles, 316 showing ventricular extrasystoles and 5 auricular paroxysmal tachycardia. These figures are doubtless far from a fair average, because we examined a great number of patients suffering from toxic goiter (both hyperplastic and nonhyperplastic) and fibrillation is very common in such cases. The proportion of 16 flutters to 363 fibrillations is probably a fair average.

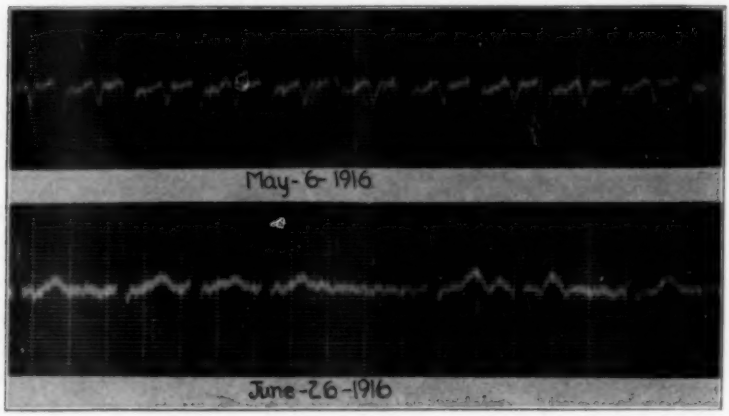


Fig. 3 (158953).—1. 2-1 flutter; auricular rate 316; ventricular rate 158. 2. Fibrillation induced by digitalis.

Symptoms.—The symptoms of the condition depend essentially on the ventricular rate and the cardiac compensation. The symptoms do not depend on the auricular rate alone, for the auricles may be found at 320 and the patient may not be aware of serious trouble, or the auricles may be dilated and functionally inactive (fibrillation) yet with good cardiac compensation and with little or no discomfort. Symptoms are further confused by disease to which the flutter is incidental or terminal, as in mitral disease, arteriosclerosis or chronic nephritis. In

15. Lewis, T.: Observations on a Curious and Not Uncommon Form of Extreme Acceleration of the Auricle. "Auricular Flutter." Heart, 1912-1913, **4**, 171. Mackenzie, J.: Diseases of the Heart. Ed. 3, London, 1913, p. 105. Ritchie, W. T.: Auricular Flutter. Edinburgh, Green, 1914, p. 33. Rihl, J.: Klinische Beobachtungen über atrioventriculäre Automatie mit Bradykardie. Ztschr. f. exper. Path. u. Therap., 1911, **9**, 496. Gibson, G. A.: A Discussion on Some Aspects of Heart Block. Brit. Med. Jour., 1906, **2**, 1113.

such cases flutter is clearly a manifestation of serious nutritional disturbance in the auricular wall and should be regarded only as a symptom worthy of relief.

Flutter cases may be conveniently classified as paroxysmal or chronic, depending on the duration of the disorder. We use the term "paroxysmal" in cases in which the normal rhythm is restored between attacks lasting a few hours or days and "chronic" when the condition tends to persist.

Paroxysmal flutter is not clearly defined from auricular paroxysmal tachycardia, as before mentioned. We have observed it only as a disorder incidental to evident myocardial disease; it is serious because of the great strain on the myocardium. Short paroxysms of flutter occur in which the auricular rate is between 200 and 380 and the ven-

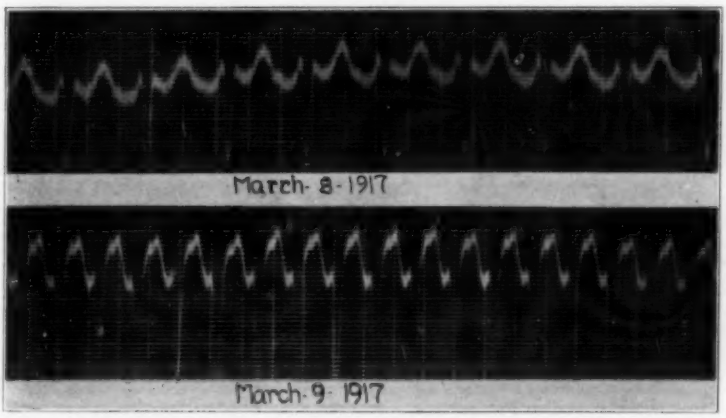


Fig. 4 (187575).—1. 2-1 flutter; auricular rate 224; ventricular rate 112. 2. Paroxysm of 1-1 flutter; rate 232.

tricular rate bears a definite or indefinite ratio to the auricular. The attack gives symptoms of cardiac embarrassment varying in degree with the cardiac compensation and the length of the attack. Palpitation, tachycardia, flushing, breathlessness, weakness, flatulence, pallor, vertigo, polyuria, faintness and syncope come on as the attack progresses, though sudden relief may come at any time from cessation of the attack. We have seen, alternately, attacks of flutter and fibrillation in the same patient.

Chronic flutter should always be recognized, for it can usually be relieved. The flutter lasts for long periods, for weeks or even years, and can be detected by proper tracings at any time during its course. The ordinary auriculoventricular ratio is 2-1 and the pulse is usually

100 to 180, but any degree of block may exist. The pulse, therefore, may vary from idioventricular rhythm, 32, to the full auricular rate, 320.

The most constant symptoms in our cases have been persistent and obscure tachycaria and weakness. Most of the patients are subject to "weak spells"—violent paroxysmal attacks of tachycardia with acute cardiac insufficiency brought on usually by exertion and by stopping suddenly. In such paroxysms the ventricles assume or approximate the auricular rate. Certain patients have described it as "a feeling like a bird fluttering in the chest," which is probably a fairly characteristic sensation. An occasional patient is very little inconvenienced by the paroxysm and in such instances the trouble is most likely to be overlooked.

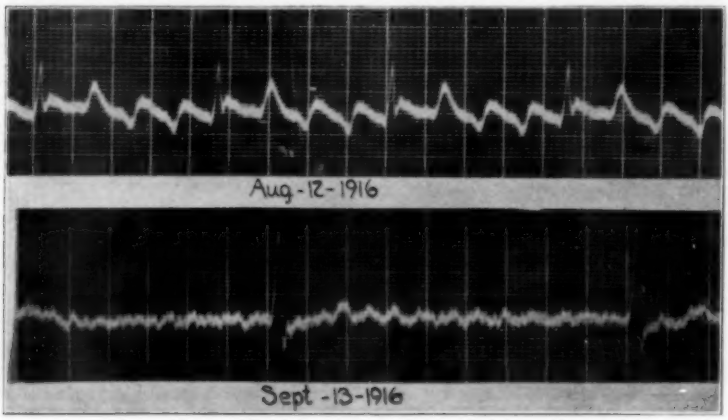


Fig. 5 (168507).—1. 4-1 flutter. 2. Fibrillation with complete heart block under digitalis.

Objectively, the heart may be normal except for weak sounds and a tick-tack rhythm. Usually there is a tachycardia more or less marked, and often there is mitral stenosis. In one half of our cases the pulse has been regular and in the others markedly irregular, owing to regular or irregular conduction through the auriculoventricular bundle. Rapid, regular venous pulsation in the neck is indicative of the disorder; and any patient more than 30 years of age with a tachycardia unaccounted for, and particularly if he is subject to "weak spells," should be under suspicion.

Vagal Pressure.—In certain cases vagal pressure will promptly reduce the ventricular rate by increasing the degree of block; but the auricular rate is not affected by this procedure, contrasting sharply

with the cases of auricular tachycardia in which sinus rhythm is suddenly restored by vagal pressure. The slowing of the ventricle is but transitory, and is recognized as due to increasing the degree of block temporarily by causing vagal depression of the auriculoventricular bundle.

The diagnosis rests finally on graphic tracings, and we believe the electrocardiograph to be far the most satisfactory. While we disclaim expert knowledge of the polygraph, we feel sure that the findings with this instrument may easily be misinterpreted and are not invariably conclusive.

SUMMARY OF CASES

Following is a brief summary emphasizing the interesting features in our cases:

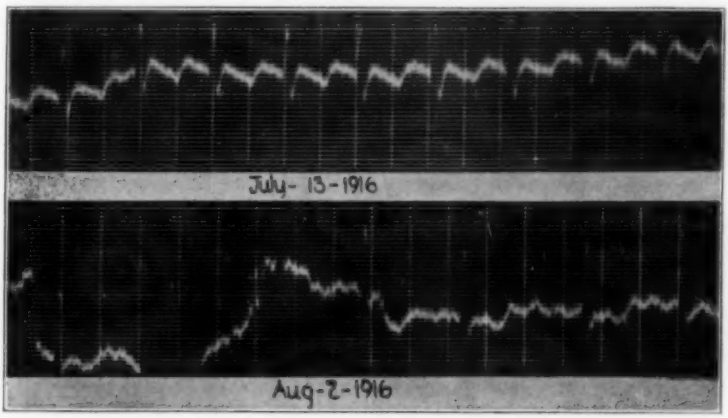


Fig. 6 (92324).—1. Auricular flutter; auricular rate 292; ventricular rate 146. 2. Fibrillation induced by digitalis; rate about 120.

Case 119641.—A man, aged 39, came for examination Nov. 24, 1914. He had suffered with hay-fever for years, and with asthma during the past year. He came to the clinic during a paroxysm of tachycardia which had existed for two days. The pulse was 212 constantly, with marked evidence of cardiac embarrassment. These attacks had occurred twice within the year and had lasted six and eight days, beginning and terminating abruptly. He was unable to retain any medicine, and in spite of the treatment died on the fifth day of his attack, three days after his arrival. Before death the heart was greatly dilated and the pulse varied instantly from slow to rapid rhythm. No tracings were possible after the first day. No valvular lesion was demonstrated clinically or pathologically.

Case 142236.—A man, aged 55, was admitted to the clinic Sept. 28, 1915. The patient had been subject to "grippe," and five years before coming for examination had noticed dyspnea and spells of syncope with sudden onset. He would fall whenever and wherever the spells came on. At this time he rested six weeks and improved. One year later (July, 1913) he had another attack which

lasted six weeks and which necessitated two weeks in bed. April, 1914, another attack lasted a month, after which his health was good until July 7, 1915, when a sudden attack came on while he was eating supper. This had persisted since with violent attacks of syncope. During the first examination in the clinic the patient suddenly went into collapse. He became cyanotic, pulseless and unconscious; there was extreme pallor and cold sweat. Death seemed imminent, when the idea of vagal pressure suddenly occurred to one of us. Pressure on the right vagus suddenly reduced the pulse rate (see cardiograms of similar pressure in another attack) to about 55, with prompt recovery of consciousness. Fibrillation was induced three times during two months by digitalis therapy, only to have the flutter recur after its discontinuance. The patient's fortitude in attempting a fourth course of treatment was rewarded by a return to a sinus rhythm on Christmas eve, and eighteen months later he reported that he was

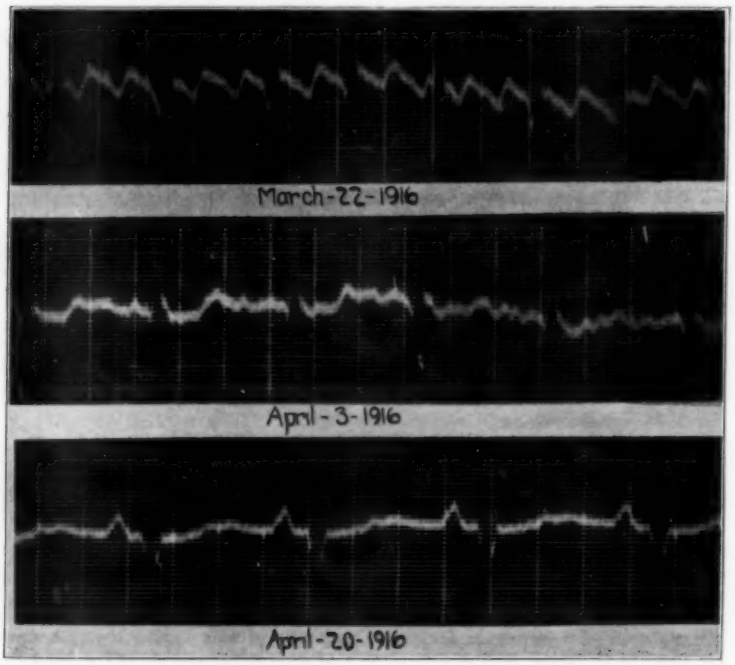


Fig. 7 (145990).—1. Auricular flutter; 2-1 rhythm; auricular rate 340; ventricular rate 170. 2. Fibrillation induced by digitalis. 3. Sinus rhythm following thyroidectomy; rate 92.

doing light farm work. The heart was normal objectively between attacks except for occasional auricular extrasystoles.

Case 142802.—A woman, aged 32, was admitted to the clinic Oct. 6, 1915. She had had repeated tonsillitis and a probable exophthalmic goiter. She came for relief from biliary colic. For several months she had been conscious of a "fluttering heart" and had had several spells of violent palpitation, usually following exertion. Electrocardiograms showed a 320-160 rate ordinarily. While under observation she came into the office with a ventricular rate of 320 (counted

by stethoscope) during a paroxysmal attack lasting nearly two hours. She had walked several blocks to the office and was not sufficiently inconvenienced during the first hour to make complaint. The rapidity was discovered on examination, when the ventricular rate was found to have fallen to 300. She walked up one flight of stairs for a cardiographic examination during the attack, which stopped suddenly while the examination was in progress and the usual 2-1 rhythm was reestablished. This case is unique in that it is the fastest human

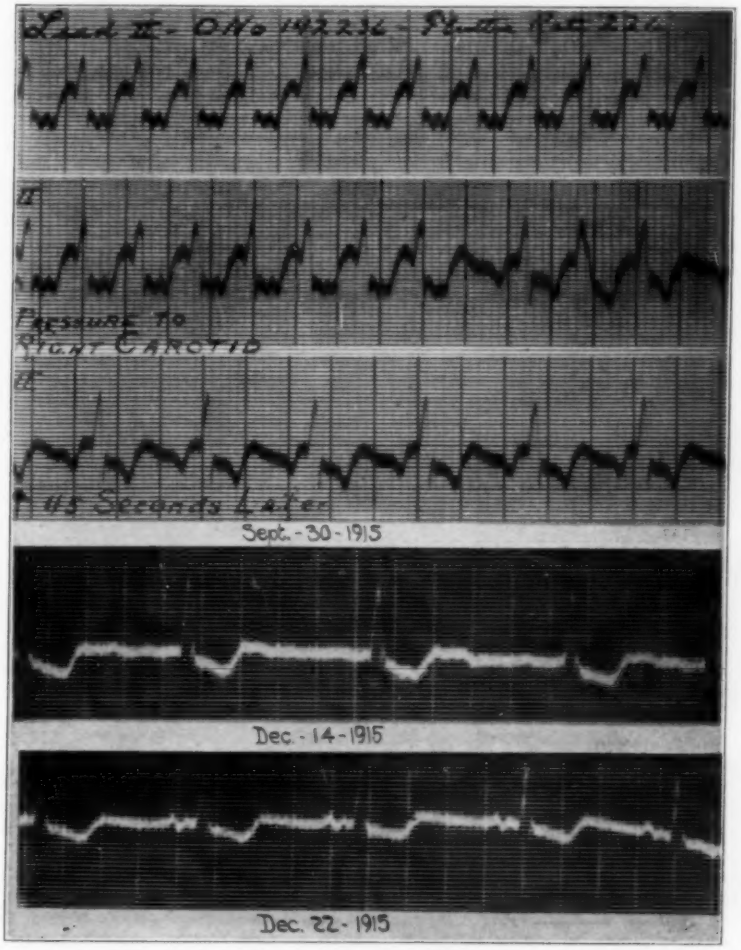


Fig. 8 (142236).—1. Paroxysm of 1-1 flutter with 45 second intervals between the three strips; rate 224; pressure applied to right vagus indicated by arrow at beginning of second strip; 2-1 flutter established within a few seconds, as indicated in third strip. 2. Fibrillation induced by digitalis; rate; 88. 3. Sinus rhythm restored; rate 71; definite abnormal auricular rate.

ventricular rate yet recorded. The patient said she had suffered from such attacks repeatedly and that the present attack was milder than many of the others.

Under digitalis medication fibrillation was induced but on its withdrawal flutter returned. A second trial resulted similarly; a third attempt was made, and the patient while fibrillating was referred for cholecystectomy, which was successfully accomplished. A sinus rhythm was established some days later (rate 120) and persisted for four months, until the flutter returned following heavy work cleaning house. We obtained further tracings May 1, 1916, showing flutter, but the patient could not remain for treatment.

This case had been diagnosed as exophthalmic goiter before the patient came to us and she was anxious to have a thyroidectomy. We wished to defer operation on account of the heart condition and the questionable diagnosis of hyperthyroidism, and thyroidectomy was performed elsewhere (November, 1916). Pathologic examination of the tissue, which the surgeon kindly sent to us, showed the typical hyperplastic changes of exophthalmic goiter. The patient reports a pulse practically normal and health restored since operation.

Case 145990.—A woman, aged 41, came for examination March 21, 1916. The patient had had tonsillitis repeatedly. She had had the classical symptoms

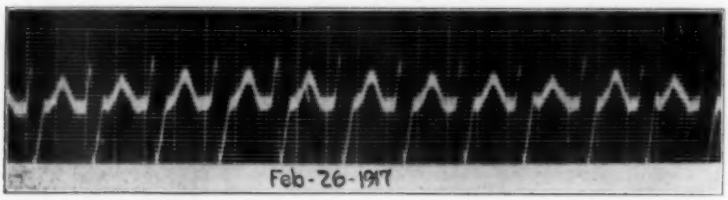


Fig. 9 (130119).—Auricular flutter; auricular rate 300; ventricular rate 150.

of exophthalmic goiter for four years. Three months previously ligations had been done in the clinic. No cardiac disorder was then suspected. On returning for thyroidectomy she was prostrated by a prolonged paroxysm of tachycardia. The cardiogram revealed flutter. She was treated with digitalis, and thyroidectomy was done while the heart was fibrillating. Sinus rhythm was restored soon after operation. She gave the interesting history of a prolonged paroxysm of tachycardia the year before, during which syncope was so complete that she was thought to be dead. Aug. 10, 1917, the patient reported marked improvement in general health and no more spells of tachycardia.

Case 146153.—A man, aged 26, entered the clinic March 18, 1916. There was no history of previous infections, except typhoid in 1912. The tonsils appeared large and unhealthy. Classical exophthalmic goiter with symptoms had existed for nine years; relatively mild symptoms until the last two years. He had had three spells of vomiting and prostration, probably due to flutter. The heart action had been irregular and rapid but no record was taken before the ligations were done here Nov. 26, 1915. At the present examination the cardiogram showed typical auricular flutter. Heavy digitalis medication, 29 c.c. in ten days, brought on fibrillation. Thyroidectomy was performed April 10, 1917, and sinus rhythm was restored shortly after. The patient reports Aug. 7, 1917, "I have forgotten all about my heart."

Case 168507.—A man, aged 43, was examined Aug. 9, 1916. The patient gave a history of typhoid and he was subject to tonsillitis. He came to the clinic because of recurrent attacks of appendicitis. He appeared healthy. A cardiographic examination was made on account of the irregular pulse. After discovering the flutter we elicited a good history of sudden attacks of mild

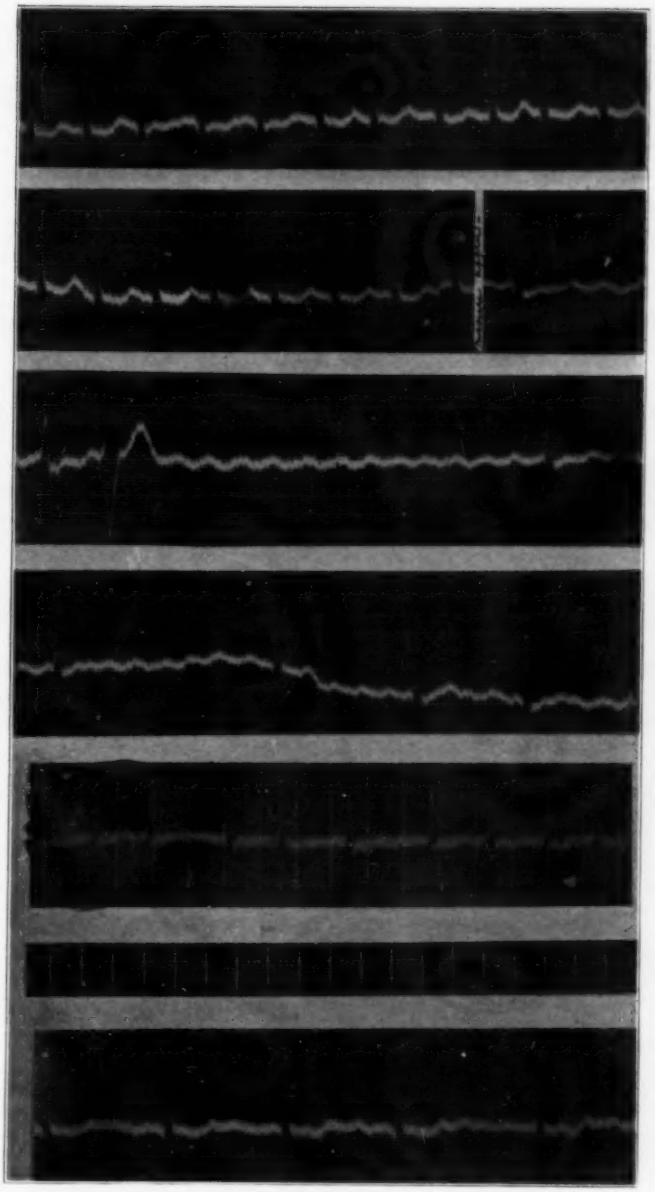


Fig. 10 (195883).—1. Auricular flutter; 2-1 rhythm. The top five strips are continuous tracings cut for reproduction. Pressure applied at point indicated by interruption of light; cessation of ventricular action 4.5 seconds in third strip on release of pressure; series of ventricular extrasystoles as shown in fifth strip before resumption of normal rhythm. 2. Lowest strip shows fibrillation under digitalis.

syncope with rapid heart action, brought on by marked exertion during the previous five years. Mild chronic dyspnea was also admitted. The patient was treated thirty days, taking 100 c.c of digitol before complete heart block and fibrillation were induced. He left us then, but he has reported through his brother (Aug. 12, 1917) that he feels well. The appendix has not been removed.

Case 158953.—A man, aged 61, was examined May 5, 1916. Twelve months before admission, following grippe and mumps, the patient had had "nervous prostration," chief symptoms, nervousness, weakness and palpitation. His physician told him the rapid pulse was due to "nervousness." November, 1915, there was again a sudden onset of rapid heart and weakness which has persisted to date. He had "weak spells" and was dizzy. With rapidity of the heart hoarseness was noticed. He was treated with 69 c.c. digitalis twenty-three days before the onset of fibrillation. Flutter recurred and the treatment was again instituted for a few days until the onset of fibrillation. A few days later there was a second recurrence of flutter and again fibrillation was induced by digitalis. Tonsillectomy was performed July 10 without incident. The patient continued

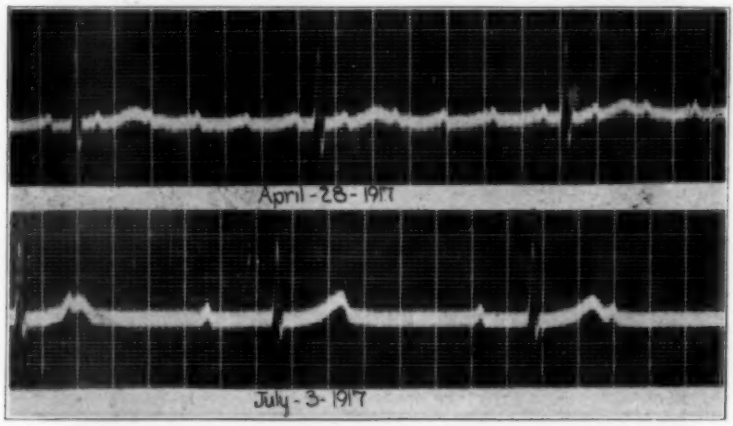


Fig. 11 (192392).—1. Auricular flutter with complete heart block; 5-1 rhythm. 2. Complete heart block.

fibrillation without cardiac symptoms up to the last report. From subjective sensations he was able to say accurately whether flutter or fibrillation was present. No evidence of cardiac hypertrophy or valvular disease was obtainable at any time.

Case 161186.—A man, aged 75, a feeble, stiff, fat old man with marked sclerosis of the peripheral vessels and evident cardiac insufficiency, was examined May 31, 1916. He dated rheumatic symptoms back to rheumatic fever twelve years and four years previously. Dropsy had been noted for a year but not much dyspnea or palpitation, probably because the rheumatism made exertion difficult. Blood pressure 170-82 and pulse varying from 44 to 68, indicating impaired auriculoventricular conduction. There was no valvular disease evident and the heart was not definitely large. Treatment by rest and digitalis at home was recommended.

Case 92324.—A woman, aged 39, was admitted for examination July 12, 1916. Definite exophthalmic goiter; ligation performed in the clinic, October, 1913. At this time the pulse was regular, 95 to 118, and the heart greatly dilated.

Thyroidectomy was performed, February, 1914, after marked improvement in the heart condition. The patient returned the second time for observation. All of the previous winter she suffered from frequent colds and grippe. There was no history of syncope. The first cardiogram taken showed flutter with 2-1 rhythm, ventricular rate 196. Fibrillation was readily brought on with digitalis and continued during fifty-six days of observation.

CASE 130119.—A man, aged 52, was admitted for examination Feb. 17, 1917. The patient had been operated on in the clinic, May 6, 1915, under local anesthesia for a small cyst of the tongue, but no general examination had been made at that time. The patient was very obese, with evident marked cardiac

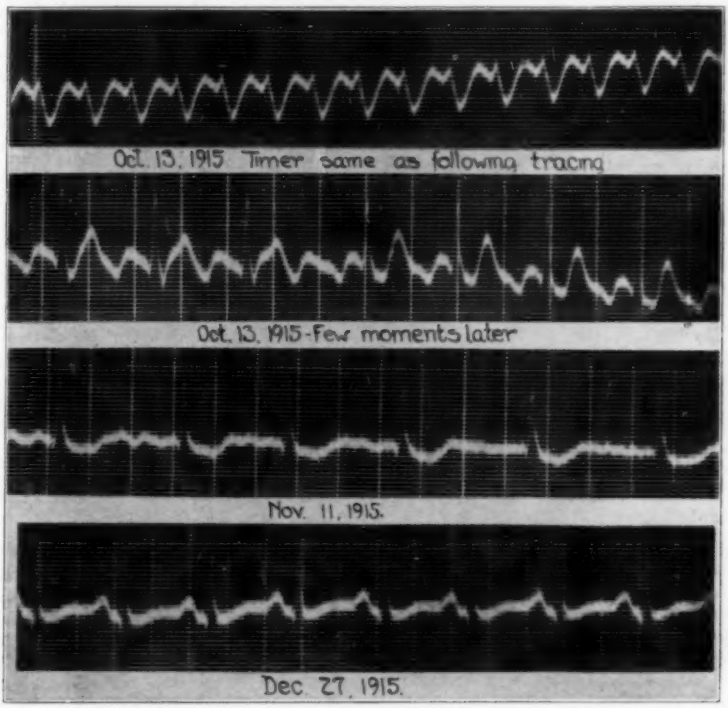


Fig. 12 (142802).—1. Paroxysm of auricular flutter showing ventricular rate slightly above 300; timer same as next tracing. 2. A few seconds later showing break in attack during the time necessary to change plates. 3. Auricular fibrillation induced by digitalis. 4. Sinus tachycardia; rate 130 following cholecystectomy and tonsillectomy. This patient was operated on subsequently elsewhere for exophthalmic goiter four months following and at present reports normal heart action and pulse rate.

insufficiency, and the roentgen ray showed diffuse dilatation of the aorta and the heart greatly enlarged. Dyspnea had been noted twelve years, but marked cardiac insufficiency followed grippe last fall. The cardiogram showed flutter. The patient died suddenly on the fourth day in a coughing attack. Necropsy revealed a fatty, dilated heart, and fatty sclerosis and dilatation of the aorta.

CASE 195883.—A woman, aged 43, was admitted for examination July 1, 1917. The patient was subject to grippe. She had had ten children. The rapid heart action had been first noticed fourteen years previously during pregnancy. There had been palpitation since on exertion, and last year there were repeated spells of very rapid heart action with palpitation. Objectively the patient showed marked tachycardia (192). Pressure on the right vagus immediately slowed the pulse to about 60; releasing the pressure permitted the pulse go back to 192. She was treated with large doses of digitalis, and fibrillation was brought on in a few days. Fibrillation continued since. A slower pulse is definite evidence of double mitral lesion.

CASE 187575.—A man, aged 45, was admitted for examination March 8, 1917. He had had typhoid twenty-seven years previously. For two years he had been subject to attacks of dyspnea and pain in the precordium radiating to the epigastrium. Worse attacks lasted one-half hour, causing complete incapacity. The heart enlarged objectively but no valvular defect was noted. The electrocardiogram showed typical flutter, auricles 224, ventricles 112. The second examination showed ventricles 224, and a 1-1 rhythm. The patient was unable to remain for treatment.

CASE 192392.—A man, aged 37, was admitted for examination Aug. 25, 1917. He gave a history of a questionable sore on the penis at the age of 17, but we were unable to establish syphilis on a most searching investigation. Apparently the man was strong and healthy. There had been mild dyspnea on exertion for two years, but no definite attacks. A month previously a sudden syncope followed very heavy lifting and the "right arm went dead for a little while." The heart was objectively negative except for a slow pulse (46). The electrocardiogram showed flutter, auricles 225 and ventricles 46. To rule out syphilis a therapeutic test was given, with no result after three weeks of treatment. Digitalis was started and the next morning a second cardiogram showed a sinus rhythm with complete disassociation of ventricles (46) and auricles (72). The digitalis was stopped at once. The condition had persisted since (three months). No further medication was used except potassium iodid for empirical reasons. The patient suffered no subjective inconvenience and had no evidences of a Stokes-Adams syndrome.

CASE 145519.—A thin, asthenic woman, aged 30, was admitted for examination Aug. 2, 1917. Following pneumonia five years previously she had suffered with repeated weak spells associated with rapid heart action. The pulse was always rapid, and at the examination averaged 133. Electrocardiogram showed auricular flutter, auricles 266, ventricles 133. This patient is to return for treatment.

CASE 204974.—A man, aged 37, was admitted for examination Aug. 17, 1917. The patient had been asthmatic all his life, but we were unable to elicit a history of previous infection. He was a laborer and looked robust. The heart had been very rapid for three years when at work, but there was no history of weak spells. He was prepared for a cardiogram on account of irregular pulse. Auricles 258. Ventricles 172. This patient is to return for treatment.

CASE 203875.—A thin man, aged 52, was admitted for examination Aug 6, 1917. He was subject to colds. Eight years previously he had an attack called "bilious" for three weeks. The muscles were contracted and there was debility and weakness with sudden onset. Morphin relieved the attack. Since then repeated lighter "bilious spells" occurred and morphin was given to prevent the spasm. These attacks occurred at intervals of weeks or months. Podophyllum or morphin relieved the attacks. There was mild chronic dyspnea and the electrocardiogram showed flutter. The patient continued under treatment.

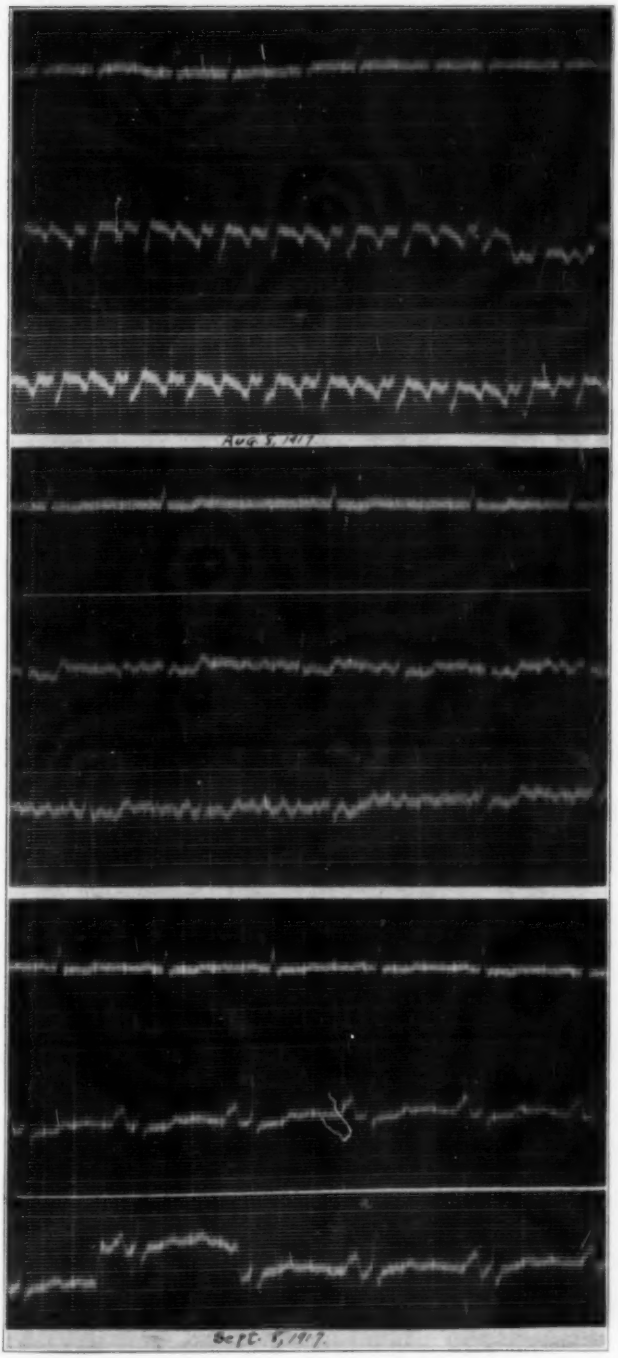


Fig. 13 (203875).—1. Paroxysm of auricular flutter showing ventricular rate of 120. 2. Twenty-six days later showing auricular fibrillation after heavy digitalis dosage. 3. Sinus rhythm five days later.

Treatment and Results.—As Lewis has shown, digitalis has proved to be the sovereign remedy in cases of flutter. We have used the drug in large doses, and have treated ten patients, not counting the two who were moribund and who died before any effect of medication was possible. Two patients (Cases 161186 and 192392) were not treated for obvious reasons, and two (Cases 204974 and 187575) were unable to stay for treatment.

The amounts of digitalis administered and a summary of the results are given in the accompanying table. All the patients were in the hospital at complete rest during the digitalis medication. Digitalis broke the flutter in all ten patients, and four finally resumed and held a normal rhythm. The others were markedly improved subjectively by the onset of fibrillation.

TABLE SHOWING AMOUNTS OF DIGITALIS GIVEN AND SUMMARY OF RESULTS

Case	Onset of Fibrillation		Onset of Toxic Effects	
	Days	Amount, C.c.	Days	Amount, C.c.
142226	75	280	51	185
142802	42	220	28	180
145090	60	94	0	0
146158	8	29	0	0
158968	51	100	22	70
922324	4	12	0	0
168507	23	100	0	0
195823	16	51	0	0
202875	84	190	22	100

The most important point in the treatment is to use enough digitalis. We have run up the dose rapidly to the physiologic tolerance of the patient. Our maximum dosage was 10.5 c.c. daily for ten days before toxic effects were evident. We have seen no bad results from such massive dosage except the temporary toxic symptoms, and we feel sure that most patients require massive dosage to obtain the desired result. Further, we have found better results from pushing the drug to physiologic complete block if the patient tolerates it to this point; that is, far beyond the point of fibrillation in most instances. In all our patients we have produced marked poisoning before discontinuing the drug. In the four cured patients we repeatedly had the fibrillation break back to a flutter until digitalis poisoning was produced.

The after-treatment is important. We discontinue medication for cured patients, but have advised in fibrillating cases that digitalis be used, if necessary, to keep the pulse averaging below 80 when at rest. The usual general advice to cardiopaths should always be emphasized.

Operability.—One operation is reported in the literature—a death on the table under chloroform anesthesia attributed to flutter. We believe that if surgical treatment is indicated, particularly the removal of a probable source of infection or toxemia, the risk should be accepted. All operations have been performed after inducing fibrillation by digitalis and while the patient was under medication. We have been careful not to have atropin administered before operation, since this would temporarily abolish the vagus stimulation of the digitalis.

Three of our patients had exophthalmic goiter, and in two of these sinus rhythm and apparently normal health were regained after thyroidectomy. The third was a bad cardiopath, but sinus rhythm was restored, though the patient still has some symptoms of cardiac insufficiency.

Removal of the tonsils seemed advisable in cases in which there was evident focal infection, and this was done in two instances. One patient improved greatly; the other is subjectively cured. Cholecystectomy was done in one case.

SUMMARY

Auricular flutter occurs as a mechanical disorder in certain diseased hearts, and in our experience has been most frequently associated with exophthalmic goiter.

The paroxysmal attacks noted in fourteen of our sixteen cases are dangerous to health and even to life. Two patients died in such attacks and two others appeared so nearly dead as to deceive competent observers. The patient with flutter is always in danger of such attacks. He should always have the disorder arrested as soon as possible after its discovery.

In our experience efficient treatment may be relied on to cause the onset of fibrillation and greatly to relieve the patient. None of our patients is known to have had a recurrence of flutter after his dismissal.

Three patients were operated on under ether anesthesia for exophthalmic goiter after fibrillation was established, and one of these and one other have had tonsillectomies (local anesthesia) performed without incident. Cholecystectomy has been performed in one case.

All of the ten treated patients are alive and much improved or cured with treatment. Five report that they cannot detect any cardiac symptoms.

HEART-BLOCK

I. TWO CASES OF COMPLETE HEART-BLOCK SHOWING UNUSUAL FEATURES *

FRANK N. WILSON, M.D., AND G. CANBY ROBINSON, M.D.
ST. LOUIS

The following two cases of complete heart-block are considered worthy of report because of several unusual features shown by electrocardiograms.

REPORT OF CASES

CASE 1.—Mrs. E. P., an American housewife, aged 39, had been under observation in the Washington University Dispensary for two years. She first came to the dispensary because of various gynecologic complaints associated with retroversion of the uterus. At that time it was found that she had an unusually slow pulse rate, and electrocardiograms revealed the presence of complete heart-block. This condition had been constantly present since, but in spite of this fact she had had no cardiac symptoms aside from slight dyspnea on exertion. She had never had a syncopal attack. Physical examination of her heart had constantly shown moderate enlargement of the cardiac dulness, the presence of an apical systolic murmur transmitted to the axilla, and a faint aortic systolic murmur poorly transmitted. The patient's past history revealed no infections which might account for the cardiac condition aside from frequent attacks of tonsillitis during childhood. The Wassermann reaction was negative. When she was 19 years old, she was told by a physician that her pulse rate was only about one half the normal, so that it seems likely that the heart-block had been present for at least twenty years.

CASE 2.—Mr. M. R., a German cigarmaker, had been under observation in the Barnes Hospital and the Washington University Dispensary since March 31, 1917. He presented himself on that date complaining of syncopal attacks, vertigo, and dyspnea on exertion. During the previous seven weeks he had had five syncopal attacks of short duration, all of which came on without warning and without any apparent exciting factor. None of these attacks followed exertion. Between attacks he was troubled by vertigo on turning quickly and by dyspnea on exertion. Physical examination revealed moderate enlargement of the cardiac dulness and a faint systolic murmur was heard over the whole precordium. The heart was beating regularly at the rate of 36 per minute. There was a moderate arteriosclerosis. Electrocardiograms showed the presence of complete heart-block. The past history and the laboratory findings, including the Wassermann reaction, were negative.

DISTURBANCES OF AURICULAR ACTIVITY

The electrocardiograms revealed a tendency in both patients for those interauricular periods during which a ventricular systole occurred to be shorter than those which followed them (Figs. 1 and 2). This

* Submitted for publication Sept. 1, 1917.
* From the Department of Internal Medicine, Washington University Medical School.

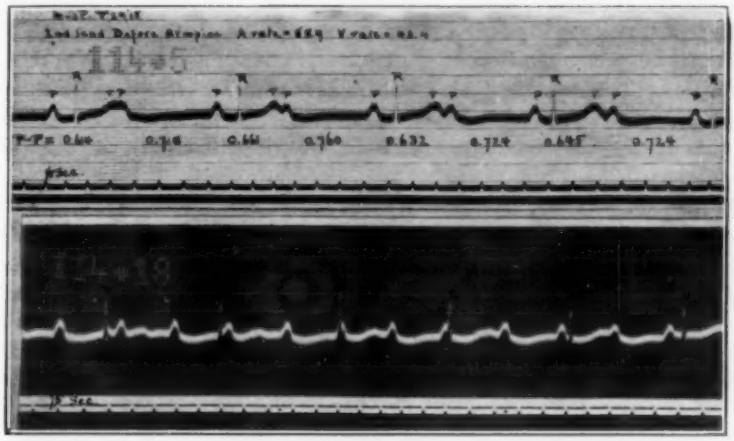


Fig. 1 (Case 1, Lead II).—Complete heart-block. Atropin produced an acceleration of both the auricular and ventricular rates and caused the auricular arrhythmia to disappear.

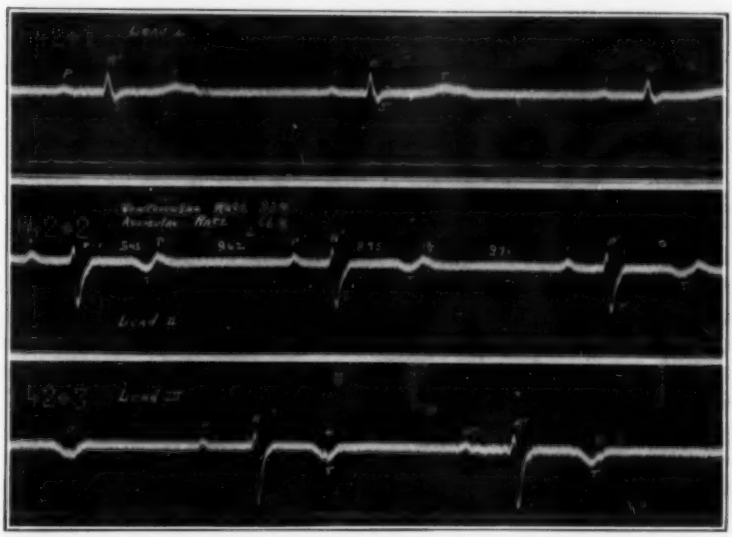


Fig. 2 (Case 2).—The usual cardiac mechanism. Complete heart-block; auricular rate 66.8, ventricular rate 33.4. Those auricular periods which contain a ventricular contraction are shorter than the others.

tendency was observed only when the auricular rate was comparatively slow; it was not definitely present when the auricular rate was rapid, as after exercise or after the administration of atropin (Fig. 1). This type of auricular arrhythmia has been previously described by Hecht,[1] who observed it in a case of complete heart-block in a child. This author offers no explanation for its occurrence. Erlanger and Blackman[2] have described a similar auricular arrhythmia in experimental heart-block. They found that each ventricular systole produced a marked slowing of the auricular rate. In marked instances this slowing was so great that only one auricular beat occurred during each interventricular period; when several auricular beats occurred between two consecutive ventricular beats, the first interauricular interval was long and the following auricular periods became gradually shorter. Erlanger and Blackman ascribed this type of auricular arrhythmia to

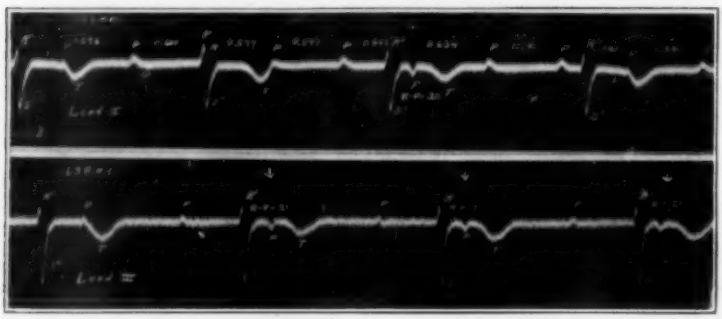


Fig. 3 (Case 2).—Ectopic auricular beats represented by inverted auricular complexes occur when an auricular contraction is due shortly after the beginning of ventricular systole.

rhythmical "variations in vagal tone, vagus inhibition increasing with each arterial pulse and diminishing again between pulses." It is quite possible that the auricular arrhythmia observed in our patients was the result of a similar mechanism. The absence of the arrhythmia when the heart rate was fast after exercise and after atropin (Fig. 1) lends support to the view that it was dependent on vagus activity.

The occurrence of another type of auricular disturbance in one of our patients leads us to believe, however, that another explanation of this arrhythmia is possible. In Case 2 a peculiar type of ectopic beats frequently occurred. These beats are represented in the electrocardiograms (Fig. 3) by inverted auricular complexes (in Leads II and III)

1. Hecht, A. F.: Ergebn. d. inn. Med. u. Kinderh., 1913, **11**, 324.
2. Erlanger and Blackman: Heart, 1909-1910, **1**, 177.

occurring from 0.20 to 0.34 second after the beginning of the QRS group of the ventricular complex. These abnormal auricular complexes appear only when a normal P wave is almost due at this point. They bear, therefore, a fairly constant relationship to both auricular and ventricular systoles. They differ from ordinary extrasystoles in this respect, and also because they occur so very late in auricular diastole. On the other hand, it is impossible to believe that they represent retrograde auricular contractions, which they somewhat resemble, because of the presence of complete heart-block. Similar ectopic beats have been observed in a case of complete and incomplete heart-block by Cohn and Fraser,[3] and these authors mention their occurrence in a case of complete heart-block studied by Parkinson. They attribute their occurrence to the mechanical effect of ventricular systole on some ectopic auricular center. In our case, as well as in that described by Cohn and Fraser, the form of the abnormal complexes indicates that this center was situated in each case, in the lower auricular or upper junctional tissues, and it seems likely that it was located in the specialized tissues to be found in that region. We must assume that ventricular systole hastened the discharge of the stimulus in this center, and it seems possible that a similar effect of ventricular systole on the ordinary auricular pacemaker may account for the auricular arrhythmia discussed in the foregoing. A careful study of the electrocardiograms has not enabled us to decide with confidence between this explanation and the one advanced by Erlanger and Blackman, which was mentioned previously.

The effect of ventricular systole on the auricular period may explain another interesting phenomenon observed in both patients. It sometimes happened — frequently and for long periods in Case 2, less frequently and for shorter periods in Case 1 — that the auricular rate was exactly twice the ventricular. Whenever this occurred, the relationship of the auricular contractions was always nearly the same, and was of such a nature that every alternate auricular complex fell on the T wave. It can be easily understood that this relationship might be brought about by a tendency for ventricular systole to bring about an auricular contraction at this point. This relationship between the positions of auricular and ventricular contractions, when the auricular rate is an exact multiple of the ventricular, may lead to the diagnosis of partial block when complete block is really present. This fact has also been noted by Erlanger.[4] It is only when the ratio of auricular rate to ventricular rate is disturbed by exertion, or some other factor, that the true cardiac mechanism becomes evident.

---

3. Cohn and Fraser: Heart, 1914, **5**, 141.
4. Erlanger: Personal communication.

In Case 1 an entirely different type of auricular disturbance was observed. This disturbance consisted in a very marked change in the form of the P wave in the third lead. The usual form of the P wave in this lead is shown in the first six cycles of Figure 4. In the seventh cycle of this figure the P wave becomes very much larger and broader. This change in the form of the P wave was observed in this patient on two occasions. Each time it was accompanied by a definite increase in the auricular rate. We have observed similar changes in the form of the P wave in other patients and in normal individuals; they are usually accompanied by a change in rate and are usually most marked in Lead III. We believe that they are due to changes in the location of the pacemaker within the sino-auricular node, similar to the change in location of the pacemaker within this node which has been shown to occur in the experimental animal under the influence of vagus stimulation.[5]

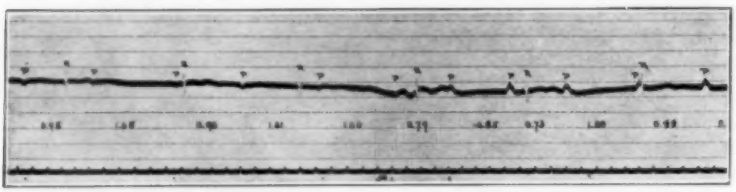


Fig. 4 (Case 1).—A spontaneous change in the form of the P wave accompanied by an increase in auricular rate.

THE VAGI AND THE IDIOVENTRICULAR RATE

There has been considerable discussion in the past as to whether the vagi exert any chronotropic influence on the independently beating mammalian ventricles. The question has been repeatedly investigated both experimentally and clinically. As a result of the clinical investigations, it has been well established that in the majority of the cases of complete heart-block, pressure on the vagus nerves in the neck and the administration of atropin do not produce any change in the ventricular rate. In a few cases, however, the administration of atropin has produced a definite ventricular acceleration. Such cases have been reported by Hecht[1] and by Hart.[6]

Vagus pressure and atropin experiments were carried out on each of our patients. Pressure on the vagi in the neck failed to affect the ventricular rate in either. The subcutaneous administration of one-

5. Lewis, Meakins and White: Phil. Tr. Roy. Soc., London, Series B, 1914, **205,** 375.
6. Hart, T. S.: Am. Jour. Med. Sc., 1915, **149,** 62.

fiftieth grain of atropin in Case 1 increased the auricular rate from 89.9 to 124.4 per minute and the ventricular rate from 43.4 to 60.0 per minute (Fig. 1). In Case 2, atropin increased the auricular rate from 74 to 96 beats per minute, but failed to affect the ventricular rate.

Two general hypotheses have been advanced to explain such findings. According to the first of these, the influence of the vagi on the idioventricular rate is dependent on the site of the lesion producing the block, and consequently on the level within the junctional tissues at which the ventricular pacemaker is located as described by Zander.[7] If this is true, in the majority of the cases of complete heart-block the lesion, and consequently the ventricular pacemaker, is situated relatively low down in a region not subject to vagus control, but in an occasional case the lesion and ventricular pacemaker are located at a higher level in a region which is normally under the control of the vagi. Organic structural lesions may occur in any portion of the His bundle, but the recent experimental work of Lewis, Meakins and White[8] indicates that functional block usually has its site in the region of the A-V node. It seems likely, therefore, that, if the influence of the vagi on the ventricular rate is dependent on the site of the lesion, the chronotropic influence of the vagi on the ventricles would be more marked in functional than in organic heart-block. There is not sufficient data at hand, however, to determine this point. The greatest objection to this whole hypothesis is the fact that the idioventricular electric complexes, which occur when complete block is brought about in animals by vagus stimulation, are usually markedly abnormal and distinctly different from those seen when complete block is produced by other means (Kahn[9]), and also different from the ventricular complexes which usually occur in clinical complete heart-block. This unquestionably indicates that the vagi do exert an influence on that region within the junctional tissues which lie above the bifurcation of the His bundle, a region which, judging from the usual form of the ventricular complexes in complete heart-block, contains the idioventricular pacemaker.

According to the second hypothesis which has been advanced to explain the established facts with regard to the vagi and the idioventricular rate, the region which contains the idioventricular pacemaker is normally subject to vagal influence, but this influence is destroyed by the same lesion which produces the block (Lewis[10]).

7. Zander, E.: Nord. med. Ark., 1915, **2**, No. 6, Part 2. Reviewed in Zentralbl. f. Herz. u. Gefässkrank., 1915, **19**, 1914.

8. Lewis, Meakins and White: Heart, 1914, **5**, 289.

9. Kahn, R. H.: Ergebn. d. Physiol., 1914, **14**, 1.

10. Lewis, T.: Lectures on the Heart, New York, Paul B. Hoeber Company, 1915.

This might easily occur if, as is probable, the majority of the vagus fibers reach the ventricles by way of the A-V bundle. Advocates of this theory have, so far as we know, not attempted to explain the occurrence of cases, such as one of those which we are reporting, in which, in spite of the presence of complete block, the ventricular rate is subject to vagal influence. The occurrence of such cases is, however, not an insuperable objection to the theory, for it has been shown by Garrey[11] that the passage of the excitation wave through a layer of muscle may be interrupted by compression without preventing the passage of nerve impulses through the same area. It is possible also that a lesion may be so located as to interrupt the muscular without interrupting the nervous connection between auricles and ventricles.

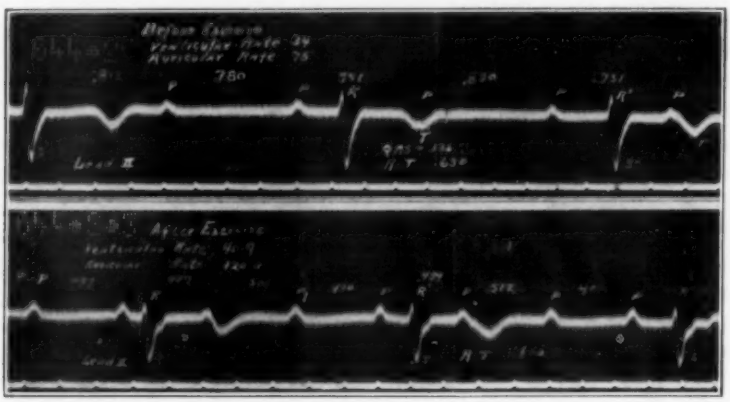


Fig. 5 (Case 2).—The effect of exercise on the cardiac mechanism. The auricular rate is markedly intensified, and the ventricular rate only slightly increased.

We also investigated the effect of exercise on the cardiac rate in one of our cases (Case 2, Fig. 5). The exercise consisted in doing 3,300 foot-pounds of work in thirty seconds by climbing stairs. Electrocardiograms were taken immediately before and after the exercise. The auricular rate was increased from 75 to 120 per minute and the ventricular rate from 34 to 40 per minute. According to Gasser and Meek[12] exercise may increase the heart rate in four distinct ways: (1) by an inhibition of vagus activity; (2) by an increase of accelerator activity; (3) by an increase in the secretion of epinephrin, and (4) by an increase in the temperature of the blood. They found that the first of these mechanisms was by far the most important. Since

11. Garrey: Am. Jour. Physiol., 1911, **28**, 249.
12. Gasser and Meek: Am. Jour. Physiol., 1914, **34**, 48.

the ventricular pacemaker in our patient was apparently not under the control of the vagi, the increase in the ventricular rate observed after exercise must have been due to the last three factors mentioned. Erlanger and Hirschfelder[13] have shown that the idioventricular rate in complete heart-block is subject to accelerator influence, and the other two factors concerned would probably act without reference to the location of stimulus production. The slight increase in the ventricular rate as compared with the marked auricular acceleration indicates the great disadvantage from which patients with complete heart-block suffer during exercise as a result of the loss of vagus control of the ventricular rate.

DISTURBANCES OF VENTRICULAR ACTIVITY

In Case 2, two distinct disturbances of ventricular activity were observed. On one occasion there was a spontaneous change in the form of the ventricular complex (Fig. 6). This was not accompanied by any definite change in rate, and two possibilities offer themselves for its explanation: there was either a change in the location of the ventricular pacemaker, or a change in intraventricular conduction at this time. This phenomenon may have been caused by a massive dose of the tincture of digitalis which had been administered twenty-three hours before it was observed.

The second disturbance of ventricular activity shown by this patient was a marked tendency to multiple ventricular extrasystoles after exertion. Multiple extrasystoles could be produced almost at will by having the patient rapidly perform about 3,000 foot-pounds of work by climbing stairs. They were first observed about twenty-three hours after the administration of a massive dose of digitalis, but could be produced as long as the patient remained under observation. The extrasystoles were not always of the same type and they occurred at a very rapid rate (Fig. 7). Single extrasystoles were observed during the same period and the number occurring in succession varied from two to eight. These extrasystoles did not occur immediately after the cessation of effort, but about two to three minutes later, and there was usually considerable variation in the form of the ventricular complex at the time of their appearance. At first it was thought that there was some relationship between the tendency to multiple extrasystoles after exertion and the administration of the digitalis, but the fact that this tendency continued unabated for a period of sixteen days after the digitalis had been given makes this relationship doubtful

It is also interesting to speculate on the relationship of this tendency to multiple extrasystoles and the syncopal attacks which the patient

13. Erlanger and Hirschfelder: Am. Jour. Physiol., 1905-1906, **15**, 153.

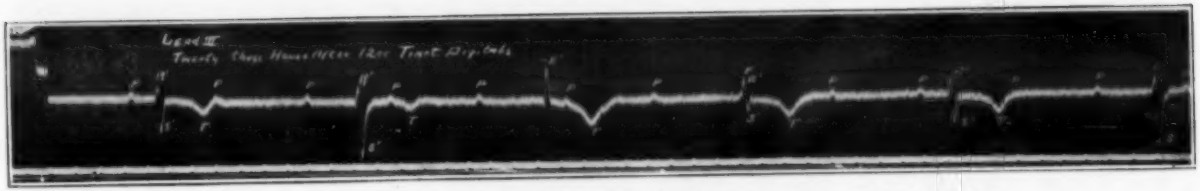


Fig. 6 (Case 2).—A spontaneous change in the form of the ventricular complex.

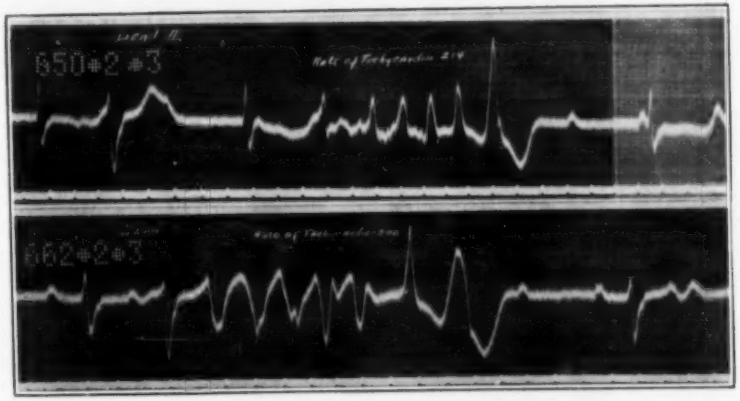


Fig. 7 (Case 2).—Multiple extrasystoles after exercise.

had. Ventricular tachycardia might conceivably produce such attacks, if sufficiently long continued, and, moreover, it is possible that the ordinary pacemaker might fail to take up the rhythm promptly after its interruption by such a series of ectopic beats as in a case observed by Lewis.[10] As the patient had no syncopal attacks while under observation, no direct evidence could be obtained on this point. Against the existence of any causal relationship between the multiple extrasystoles and the syncopal attacks is the fact that the latter never occurred after effort, while the former occurred at no other time during the period that the patient was under observation. The constant appearance of multiple extrasystoles after exercise in this case suggests that exertion may have influenced the nutrition of the heart unfavorably and thus led to their production. This idea is borne out by observations on a patient with angina pectoris who developed an idioventricular tachycardia on exertion.

SUMMARY

Two cases of complete heart-block showing unusual features are reported. The following phenomena were observed:

1. Auricular arrhythmia dependent on ventricular activity.

2. Ectopic auricular beats dependent on stimuli received from the contracting ventricles.

3. Increase in the idioventricular rate after the administration of atropin.

4. Multiple ventricular extrasystoles after exertion.

5. Spontaneous changes in the form of the auricular and of the ventricular complexes.

The explanation of these phenomena is discussed.

THE RATE OF ABSORPTION AND EXCRETION OF THE IODIDS OF STRONTIUM, SODIUM AND POTASSIUM *

E. J. KRAHULIK, M.D., AND J. D. PILCHER, M.D.
OMAHA CLEVELAND

Strontium salts have been used to a limited extent in therapeutics for the effect of the bromid, iodid or salicylate radical, but their use has been more or less discouraged because it was thought that the strontium salts were more slowly absorbed than the corresponding salts of sodium and potassium.[1]

Since all iodids would exist in the blood and tissues essentially as sodium iodid, the excretion would be the same irrespective of the cathion, provided, of course, that the other conditions were the same. Consequently, any difference in the excretion of the iodid in the urine would indicate that the change was primarily in the absorption of the original iodid. Iodid was chosen in this investigation because its normal excretion has often been determined and because its quantitative estimation is simple and accurate. The excretion of strontium iodid was compared with that of sodium and potassium.

Method.—The investigation was made chiefly on one subject, but for comparison a lesser number of experiments were made with the strontium and sodium salts, only, on two other individuals. Each subject led a fairly uniform life during the investigation. The iodid was taken immediately after a uniform breakfast and the total urine collected at the following periods: ½, 1, 2, 6, 12, 24, 48 and 72 hours. At least three experiments were made with each drug, with a minimum interval of four days between experiments to insure the complete excretion of the previous dose. The iodid was estimated by the usual methods.[2] The averages of the iodid excreted at the different periods

* Submitted for publication July 31, 1917.

* From the Pharmacological Laboratory, School of Medicine, University of Nebraska.

* The investigation was undertaken at the request of the Committee on Therapeutic Research of the Council on Pharmacy and Chemistry of the American Medical Association.

1. Cushny: Pharmacology and Therapeutics, 1915, p. 567.

2. Convenient quantities of urine (10 to 50 c.c.) were evaporated in nickel crucibles with 1 gm. potassium hydroxid and 0.5 gm. potassium nitrate per 10 c.c. of urine; fused and dissolved in water; made acid with 10 per cent. sulphuric acid and 10 drops of 10 per cent. sodium nitrite added, and the liberated iodin extracted with carbon disulphid and titrated with hundredth normal thiosulphate.

and the total excretion are given in Table 1; the percentages in Table 2. The results are graphically illustrated in Figures 1 and 2. (As the results were similar in the different subjects the excretion of one, only, is given in the figures.)

The iodid content of the salts as determined by analysis was as follows:

NaI — 0.784 gm. per gm.
SrI — 0.525 gm. per gm.
KI — 0.722 gm. per gm.

TABLE 1.—Quantity of Iodin in the Urine at the Separate Periods, and Total Excretion in Grams of Iodin

Hour	NaI 1 Gm	Total	SrI 1 Gm. (x Factor)	Total	SrI 1.5 Gm.	Total	KI 1.00 Gm.	Total	NaI* 1 Gm.	Total	SrI* 1 Gm. (x Factor)	Total
½	0.0063		0.0057		0.0053		0.0082					
1	.....	.....	.....	.....	.....	.....	.....	.....	0.0298	0.0298	0.0291	0.0291
2	0.0871	0.0934	0.0816	0.0873	0.1103	0.1156	0.1022	0.1104	0.0581	0.0879	0.0897	0.1188
6	0.2023	0.2957	0.2116	0.2989	0.2181	0.3336	0.2197	0.3301	0.2182	0.3061	0.2175	0.3363
12	0.1562	0.4519	0.1748	0.4737	0.1791	0.5126	0.1705	0.5006	0.1700	0.4765	0.1400	0.4763
24	0.1524	0.6043	0.1268	0.6005	0.1731	0.6858	0.1545	0.6551	0.1288	0.6053	0.1753	0.6516
48	0.0771	0.6813	0.0942	0.6948	0.0861	0.7719	0.0796	0.7347	0.0542	0.6595	0.0540	0.7056
72	0.0108	0.6921	0.0130	0.7078	0.0162	0.7881	0.0239	0.7586				

* Subject P.; all others from Subject K.

TABLE 2.—Average Total Iodin Excretion in Percentage of the Intake in Grams of Iodin

Hour	NaI 1 Gm.	SrI 1 Gm.	SrI 1.5 Gm.	KI 1 Gm.	NaI* 1 Gm.	SrI* 1 Gm.
½	0.8	0.72	0.68	1.0		
1	....	....	....	....	3.8	3.7
2	11.8	11.1	14.7	14.1	11.2	15.2
6	37.7	38.0	42.5	42.1	39.0	42.6
12	57.6	60.1	65.4	63.8	60.8	60.8
24	72.8	76.5	87.5	83.5	77.2	82.8
48	82.6	88.4	98.4	93.7	84.1	90.0
72	88.2	90.3	100+	96.7		

* Subject P., all others are from Subject K.

One gram of sodium iodid was the standard dose; 1.5 gm. of strontium iodid and 1.09 gm. of potassium iodid gave equal amounts of iodin. In several experiments but 1 gm. of strontium iodid was taken, so that in the tables and figures the results are multiplied by the correct factor as indicated.

Rate of Excretion.—There is practically no difference in the rate of excretion of the iodids of strontium, sodium and potassium as illustrated in Figure 1, which shows an increasing excretion rate reaching the maximum at about the sixth hour and then decreasing rapidly; during the third day but 10 to 20 mg. were excreted in all.

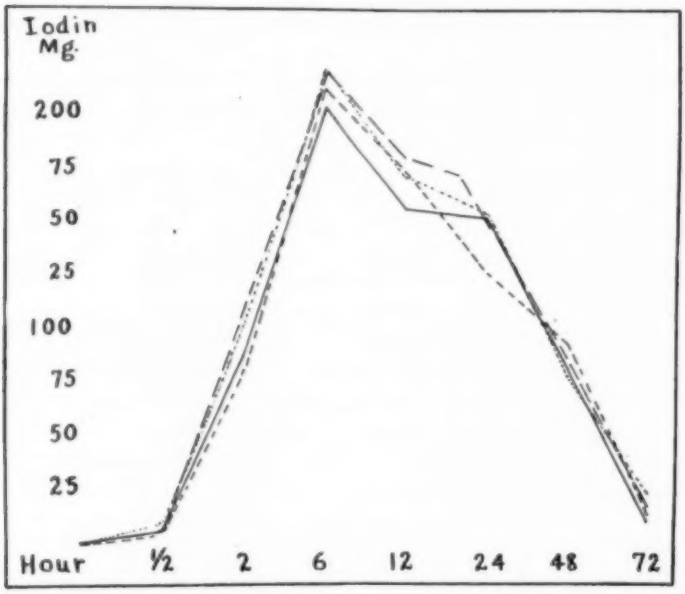


Fig. 1.—Rate of excretion of iodin in milligrams (Subject K); ——— sodium iodid; ..... potassium iodid; — — — — strontium iodid; - - - - - - - strontium iodid x factor.

Total Excretion.—A somewhat greater quantity of the strontium iodid than of the sodium iodid was excreted at the twenty-four, forty-eight and seventy-two hour periods; the potassium iodid (one subject) excretion lay between the strontium series. As can be seen from the tables and figures, the difference is slight and probably of no significance.

There seemed to be no definite ratio between the excretion of the iodid and the volume of urine. There were instances in which a

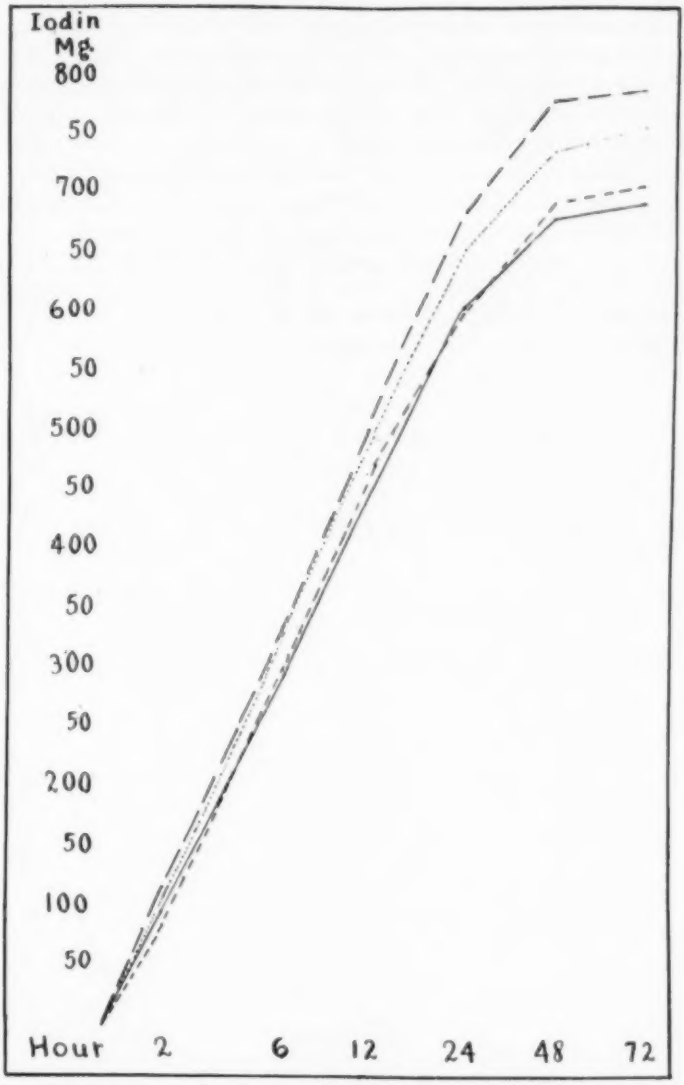


Fig. 2.—Total excretion of iodin in milligrams (Subject K); ——— sodium iodid; ..... potassium iodid; — — — — strontium iodid; - - - - - - - strontium iodid x factor.

greater volume of urine was associated with a greater excretion of iodid, but the reverse was about as frequent. The point is well illustrated in one instance of the potassium series in which the iodin excretion was strikingly uniform at the sixth hour period (225, 212 and 222 mg.) with a marked variation in the urine output (600, 205 and 270 c.c., respectively). The average volume of urine was practically the same with the different salts.

Subjective Symptoms.—About an hour after taking the iodid two subjects noticed an irritation or soreness of the pharynx which persisted for several hours and disappeared during the afternoon. There was no apparent difference from the different iodids in the time of onset, intensity or duration of the symptoms. No other symptoms were noted. The third subject noted an acne eruption of the same degree from the strontium and sodium salts.

CONCLUSIONS

The combination of iodin with strontium does not delay the excretion, and therefore the absorption, of iodin over that of sodium and potassium. In fact, both the rate and total excretion seem to be slightly greater with the strontium iodid, although the difference seems immaterial.